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Therapy Insight: the use of antirheumatic drugs during nursing

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SUMMARY

In 90% of cases, women with rheumatoid arthritis suffer a disease flare within 3 months of delivery of their baby. Drug treatment is, therefore, required; however, such therapies have implications for mothers who decide to nurse their infants. Unfortunately, because of a paucity of data, little is known about the transfer of antirheumatic drugs into breast milk, and even less is known about whether small amounts of these agents ingested during nursing could harm the infant. Our review of the literature indicates that paracetamol, prednisone, antimalarial agents, sulfasalazine and most NSAIDs can safely be used by lactating mothers. Expert opinions differ regarding the use of azathioprine, ciclosporin, and methotrexate during lactation because of varying views on the potential for short-term and long-term adverse effects. Evidence regarding the transfer of leflunomide and biologic drugs into breast milk is insufficient; therefore, until more studies are conducted, the use of these drugs in breastfeeding mothers should be restricted. At present, many patients feel they have to choose between postpartum disease control and lactation. Extended studies of the transfer of antirheumatic drugs into breast milk and the resulting consequences are, therefore, urgently needed.

KEYWORDS antirheumatic drugs, breastfeeding, lactation, side effects in infants

REVIEW CRITERIA

A PubMed search of English-language journals from 1960 to the present was performed with the following terms: "lactation", "breastfeeding", and a combination of the names of specific medications with "excretion into human breast milk". In addition, the database "LactMed" and the website "Motherisk" were searched. The authors also referred to their private libraries.

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Learning objectives

Upon completion of this activity, participants should be able to:

1 Identify the prevalence of disease flare-up in women with rheumatoid arthritis (RA) after pregnancy.
2 List immunosuppressive drugs recommended for use in women with RA during lactation.
3 Identify anti-inflammatory agents least likely to appear in high levels in breast milk during lactation.
4 Describe corticosteroid levels in breast milk with maternal ingestion.
5 Describe precautions for caring for infants of lactating women with RA who use azathioprine or methotrexate.

INTRODUCTION

Although rheumatoid arthritis (RA) tends to improve in most patients during pregnancy, 90% of patients experience flares within 3 months of delivery of their baby. The postpartum reactivation of disease symptoms is equally common in patients with ankylosing spondylitis, psoriatic arthritis, and juvenile idiopathic arthritis. As a consequence, drug treatments are often required during lactation. Effective disease control is of critical importance in order to inhibit disease progression and to enable the mother to care for her baby. Breastfeeding is the best method of feeding neonates and young infants because of the nutritional, immunologic, developmental, psychological, social, economic, and environmental benefits.[1] Studies on the excretion of drugs into breast milk are rare, and primarily based on single-dose or short-term treatment. In many cases, the effects of antirheumatic drugs on nursing infants have not been studied and,

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Received 8 November 2006 **Accepted** 30 April 2007
www.nature.com/clinicalpractice
doi:10.1038/ncprheum0532

Table 1 Use of NSAIDs and paracetamol during lactation.

Drug	No. of lactating mothers in the respective studies	No. of children exposed	Estimated amount ingested by nursing child	Adverse effects reported on nursing infant
Indomethacin[5,6,7]	15+8+1	7+1	0.3–0.5% of the maternal weight-adjusted dose; 3% of the therapeutic infant dose	1 child with seizure[a]
Naproxen[8]	1	1	2–3% of the maternal weight-adjusted dose	1 child with anemia and bleeding[b]
Ibuprofen[9,10]	12+1	23	0.01% of the maternal weight-adjusted dose; 0.06% of the therapeutic infant dose	None
Piroxicam[11,12]	2+4	1+4	3.5–6.3% of the maternal weight-adjusted dose	None
Diclofenac[13]	1	0	1% of the therapeutic infant dose	No available relevant information
Ketorolac[14]	10	0	0.2% of the maternal weight-adjusted dose	No available relevant information
Celecoxib[15,16]	5+6	2	0.2–0.3% of the weight-adjusted maternal dose	None
Paracetamol[17,18,19]	4	6+1	1–2% of the maternal weight-adjusted dose; <5% of the therapeutic infant dose	1 child with rash

All drugs in this table are compatible with breastfeeding according to expert opinion or recommendations of the American Academy of Pediatrics.[2]
[a]A case report of possible indomethacin-induced seizures in a breastfed infant has been published, although the causal link between the two events is highly questionable.[7]
[b]Naproxen possibly caused anemia, rectorrhagia, and hematuria in one 7-day-old infant whose mother was also taking bacampicillin.[8]

Table 2 Drugs with insufficient data relating to safety during lactation.

Drug	Passage into breast milk	Effect on nursing child
Methotrexate[42] (1 patient studied)	After an oral dose of 22.5 mg, peak milk levels 2.3–2.7 mg/l	No data; estimated dose ingested by child 0.02% of the weight-adjusted maternal dose
Leflunomide	No data	No data
Etanercept[48] (1 patient studied)	Dose of 25 mg etanercept twice weekly, peak milk levels 50–75 μg/l	No data; estimated dose ingested by child 0.05–0.1 mg/kg body weight (i.e. <10% of therapeutic infant dose)
Infliximab[49–51]	Transplacental passage proven. Two studies detected no infliximab in breast milk, one detected a maximum milk level of 473 ng/ml	No data

It is recommended that all drugs in this table should be avoided during lactation because of insufficient data.

overall, data regarding the long-term effects on child behavior and development are lacking. In this review we discuss drugs that are commonly used to treat patients with RA; drugs that have few indications or that are no longer used for therapy—such as high-dose aspirin, gold compounds, penicillamine and cyclophosphamide—are not included. The recommendations of the American Academy of Pediatrics[2] are provided in Table 1, and drugs for which there is limited published evidence are presented in Table 2.

DRUG TRANSFER INTO BREAST MILK AND INFANT EXPOSURE

Only the unbound fraction of a drug is transferred into breast milk by passive diffusion, until concentration equilibrium with the blood is reached.[1] Drugs can also be transferred into breast milk by carrier-mediated transport. Agents with a low molecular weight that are non-ionized and lipophilic are the most likely to be transferred into breast milk by passive diffusion. By contrast, highly protein-bound drugs are unlikely to cross extensively into breast milk, since these drugs bind preferentially to serum albumin.[3] The drug concentration in breast milk relative to that in maternal plasma is called the milk-to-plasma drug concentration ratio, which can be calculated using an equation that takes into consideration the physical and chemical characteristics of the drug.[4] For most drugs, the dose below which there is no clinical effect in infants is unknown.[4] With a few exceptions, researchers arbitrarily define a value of no more than 10% of the therapeutic dose for infants as safe (or the adult dose standardized by weight if the therapeutic dose for

infants is not known—i.e. the weight-adjusted dose) in breast milk.[4] Consuming less than 10% of the therapeutic infant dose is considered clinically unimportant in healthy term infants, provided the drug has a wide therapeutic index;[4] however, premature and newborn infants have a greater risk of developing high plasma drug concentrations than older infants because of their immature hepatic and renal systems.

DRUGS THAT CAN BE SAFELY USED DURING LACTATION

The most common postpartum flare in patients with RA, psoriatic arthritis, ankylosing spondylitis and juvenile idiopathic arthritis is a relapse of arthritis with pain, stiffness, and impaired function. These symptoms can be safely treated with NSAIDs, paracetamol, or prednisone. For patients in need of immunosuppression, hydroxychloroquine and sulfasalazine are compatible with nursing.

NSAIDs and paracetamol

NSAIDs are weak acids; therefore, only small amounts of NSAIDs appear in breast milk. More specifically, low levels of indomethacin,[5–7] naproxen,[8] ibuprofen,[9,10] piroxicam,[11,12] diclofenac,[13] ketorolac,[14] celecoxib,[15,16] and paracetamol[17–19] have been reported in human milk (Table 1). Paracetamol rapidly enters the milk and results in a milk:plasma concentration ratio of 1. In general, to minimize possible adverse effects, NSAIDs or paracetamol should be taken at or shortly after breastfeeding. Drugs with a long plasma half-life, such as piroxicam, are not recommended during lactation; however, paracetamol and most NSAIDs are compatible with breastfeeding. Ibuprofen is a preferred choice as an analgesic or anti-inflammatory agent in nursing mothers because of its extremely low levels in breast milk, short half-life and accepted use in infants in doses much higher than those conferred via breast milk.[10]

Corticosteroids

Prednisone is metabolized to prednisolone, the biologically active form of this drug. The secretion of prednisolone into breast milk has been investigated in multiple studies,[20–26] including Ost and colleagues' analysis of the dose-dependent excretion after oral doses of 10–80 mg per day of prednisolone.[24] Peak milk steroid levels occurred approximately 2 hours after a dose of prednisone was taken, with a rapid decline thereafter.[21,23] Depending on the maternal dose, peak levels ranged between 106 and 317 μg/l, and the milk:plasma ratio varied from ~0.1 (with prednisolone doses of ≤20 mg) to 0.2 (with prednisolone doses of ≥30 mg).[24] Considering that the nursing child would receive less than 0.1% of the total prednisolone dose administered to the mother,[23,24] which corresponds to <10% of the infant's endogenous cortisol production, no adverse effects should be expected, even at high maternal doses. Several reports, which include a total of 21 infants who were breastfed during long-term use of prednisone, prednisolone, or methylprednisolone, have confirmed the absence of adverse effects of these drugs in children.[25–27] In one account, two infants fed by a mother treated with 10 mg prednisone daily had normal blood cell counts, no increase in infections, and above average growth rates.[27] The small amounts of corticosteroids secreted into breast milk seem to have no clinical impact on breastfed infants. No data are available on the use of dexamethasone or betamethasone in lactating women.

Hydroxychloroquine

Hydroxychloroquine has a half-life of 18–30 days, with detectable serum levels for 50 days after discontinuation.[28] Passage of hydroxychloroquine into breast milk was studied in four women, treated with 200–400 mg hydroxychloroquine daily, a few days after the start of therapy in one patient, and after prolonged therapy in three others.[28–30] Drug levels in milk reached a peak 2 hours after ingestion of hydroxychloroquine and declined after 9 hours. Concentrations of hydroxychloroquine in the milk were approximately 1 mg/l in all three women who received prolonged therapy. It was estimated that a nursing child would ingest between 0.06–0.2 mg/kg per day, or approximately 2% of the mother's weight-adjusted dose.[28–30]

The effects of daily maternal intake of hydroxychloroquine have been investigated in 19 children who were breastfed for a range of 4 weeks to 30 months.[28,31,32] No retinal, motor, or growth abnormalities during 12 months of follow-up were detected. The benefits of breastfeeding outweigh the risk of small infant doses of hydroxychloroquine in breast milk, despite the slow elimination rate and the potential for accumulation of this drug. The follow-up studies of exposed children are reassuring;[31,32] therefore, routine eye exams of breastfed children are not indicated.

Sulfasalazine

Sulfasalazine is a combination of sulfapyridine and 5-aminosalicylic acid; the former compound is believed to target the pathophysiological mechanisms of arthritis, while the latter is an effective treatment for inflammatory bowel disease. Sulfapyridine is metabolized to acetylated and glucuronidated metabolites and is responsible for most of the adverse effects of sulfasalazine. In 26 women treated with 1.0–2.6 g of sulfasalazine daily, undetectable or negligible amounts of sulfasalazine and 5-aminosalicylic acid were found in breast milk, whereas approximately 40–50% of the maternal serum concentration of sulfapyridine was detected in breast milk.[33,34] In eight breastfed infants, sulfasalazine serum levels were undetectable or very low, but sulfapyridine concentrations ranging from 1.0–4.8 mg/l were detected in the serum of five infants.[35] Another study considered the drug metabolites present in breast milk over a 2-month period of daily treatment with 2 g of sulfasalazine.[36] Multiple milk samples and nursing infant's urine were collected and analyzed for sulfasalazine and its metabolites.[36] Sulfapyridine and its metabolites, but not sulfasalazine, were present in milk, and total levels fluctuated in the range of 3.2–13.0 mg/l; the milk:plasma ratio for sulfapyridine ranged from 0.60–0.63. The levels of sulfapyridine and metabolites found in random urine samples from the nursing infants were 3–4 μg/ml—equivalent to a 24-hour excretion of 1.2–1.6 mg (30–40% of the total dose in milk).[36]

A 3-month-old infant who was exclusively breastfed developed bloody diarrhea.[37] Except for maternal treatment with sulfasalazine, no other known etiological factors could be claimed responsible for the infant's symptoms. It has been reported that 5-aminosalicylic acid causes diarrhea in breastfed infants.[38]

In conclusion, although sulfasalazine is compatible with nursing, caution is indicated in preterm infants or in babies with hyperbilirubinemia. Monitoring for possible adverse effects in breastfed infants seems prudent.

DRUGS WITH POTENTIAL, BUT AS YET UNPROVEN RISKS FOR THE BREASTFED INFANT

Therapy with azathioprine, methotrexate and ciclosporin during breastfeeding has been discouraged because of theoretical concerns, such as immunosuppression, impaired vaccination response, growth retardation, and carcinogenesis.[2] There are, however, no studies to prove that this is indeed the case. If these drugs are deemed to be unsuitable for nursing mothers, most patients with rheumatic diseases who need immunosuppressive drugs will be excluded from breastfeeding.

Azathioprine

Azathioprine and its principal metabolite 6-mercaptopurine are metabolized to 6-methylmercaptopurine, thioguanine and to 6-thioguanine nucleotides that inhibit purine synthesis. Levels of 6-mercaptopurine were studied in the breast milk of five patients who received azathioprine after renal transplantation.[25,27,39] No 6-mercaptopurine was detected in the breast milk from three women;[39] however, peak milk levels of 6-mercaptopurine were observed 2 and 8 hours after an oral dose in the other two women, corresponding to about 0.1% of the maternal weight-adjusted dose.[25] Infant serum levels were not measured. Another study measured the active metabolites of azathioprine in four mother–child pairs.[40] Therapeutic levels of 6-thioguanine and 6-methylmercaptopurine were detected in the mothers' blood samples, whereas no active metabolites were present in the infants' blood. Mothers and infants were shown to have a normal genotype for the gene that encodes the enzyme thiopurine methyltransferase excluding any significant elevations of cytotoxic 6-thioguanine metabolites that might have occurred as a result of a mutation in the thiopurine methyltransferase gene.

Studies of 17 children from allograft recipient mothers who breastfed for 6 months to 2 years and were on long-term therapy with 50–100 mg azathioprine daily, found no adverse effects in the breastfed infants.[25,27,40,41] Therapy was often combined with methylprednisolone or ciclosporin. The children had normal growth rates, normal psychomotor development, normal blood counts, and no increased frequency of infections.

Methotrexate

For the treatment of rheumatic disease, methotrexate is administered once weekly. The therapeutic infant dose is 10–15 mg/m^2. The excretion of methotrexate into breast milk was studied in one woman (Table 2): the peak milk level after an oral dose of 22.5 mg was reached after 10 hours with a milk:plasma ratio of

0.08 and a maximum milk concentration of 0.26 μg/100 ml.[42] The significance of this dose for a nursing child is unknown. The excretion of polyglutamate metabolites of methotrexate was not studied.

Ciclosporin

Studies that investigate the transfer of ciclosporin into breast milk have shown variable results. In 11 mothers administered 250–600 mg of ciclosporin daily, milk levels ranged from 36 to 418 μg/l and ciclosporin was undetectable in infant serum.[43,44–46] Yet, in a case series of five mother–infant pairs, individual average milk ciclosporin levels varied from 98 to 564 μg/l (range 45–1016 μg/l).[44] Three infants had an estimated intake of ciclosporin ranging from 0.01 to 0.08 mg/kg per day (mean 0.05, which is about 1% of the therapeutic dose). Although one term infant had therapeutic levels of ciclosporin, three infants had undetectable levels (<25 μg/l).[44] Fifteen infants who were breastfed during maternal ciclosporin administration, and usually with concurrent azathioprine and a corticosteroid, showed no adverse effects.[43,44,46] Similarly, a 2003 report by the National Transplantation Pregnancy Registry indicated no problems in 27 infants who were breastfed for a few days to 2 years during a period of ciclosporin use.[47]

Recommendations for use of azathioprine, methotrexate and ciclosporin during lactation

There is no evidence that exposure to azathioprine by breast milk causes short-term adverse effects in infants. In addition, most reports indicate that ciclosporin is present at low levels in milk and is unlikely to cause untoward effects in breastfed infants. It is possible the infant in the single known case of high ciclosporin plasma levels attained through breast milk was not able to metabolize the drug. The single weekly doses of methotrexate that are used to treat RA might not pose any significant risk to the breastfed infant. Occasional evaluation of plasma levels of ciclosporin, azathioprine or methotrexate is recommended in breastfed infants whose mothers are being administered these drugs. Monitoring for possible adverse effects by hematologic tests, or evaluation of renal function in the case of ciclosporin, and long-term follow-up of the breastfed infants would seem prudent for all three drugs.

Tumor necrosis factor antagonists

No published evidence on the effects of tumor necrosis factor (TNF) antagonists in breastfed infants is available, but a few studies have assessed whether these drugs are transferred into breast milk. Minute amounts of etanercept were detected in the milk of a lactating (but not nursing) mother.[48] Infliximab was not detected in the breast milk of two lactating mothers with Crohn's disease after infusion of 5 mg/kg or 10 mg/kg of infliximab.[49] In a woman with RA who received infliximab for 4 months postpartum, however, infliximab was detected in breast milk and its level increased after the second infusion.[50] Interestingly, the serum levels in a mother who received infliximab five times during pregnancy, with the last dose 2 weeks before delivery, were equal to the levels found in her infant 6 weeks postpartum. Since the serum levels in the child decreased steadily in spite of breastfeeding, the initial high infant serum level was assumed to stem from transplacental passage of infliximab.[51]

In conclusion, preliminary data indicate that etanercept[48] and, according to one study, infliximab[49] are detectable in small amounts in breast milk. Since the effect of these drugs on the nursing infant have not been investigated, further studies are required to assess whether maternal therapy with TNF antagonists is compatible with breastfeeding.

DISEASE CONTROL OR BREASTFEEDING?

A postpartum patient with RA might be managed with disease flare prophylaxis or with therapy initiated only when a flare occurs. The latter approach tends to ensure a longer perinatal period without interference from a drug therapy. Most of the available literature on therapy with antirheumatic drugs and lactation put a negative spin on breastfeeding whilst on anti-RA therapy. As many mothers would rather deprive themselves of therapy than deprive their child of milk, many of these patients neglect disease control in favor of lactation. Yet, for most of the negative advice given, no evidence or clinical observations support this restriction. Furthermore, the lack of data on biologic agents means that lactating patients with RA are often not treated with the most effective therapies available.

CONCLUSIONS

Most drugs used to treat women with RA or other rheumatic diseases are excreted in small amounts into breast milk. Despite this, the infant

exposure to drugs through breast milk is much lower than from maternal treatment during pregnancy. Whether amounts far below 10% of the maternal weight-adjusted dose pose a significant risk to the nursing child is largely unknown. A prospective study presented reassuring data that most maternal medication posed little, if any, short-term adverse effects on breastfed infants.[26] Moreover, NSAIDs, paracetamol, corticosteroids, antimalarial agents, and sulfasalazine are compatible with breastfeeding. Because of theoretical concerns and fears of long-term adverse effects, however, experts disagree whether azathioprine, ciclosporin and methotrexate should be taken during lactation. Furthermore, the lack of data necessitates that mothers treated with methotrexate, leflunomide or TNF antagonists should breastfeed only after informed consent and while their infant receives regular monitoring. In general, drug exposure can be reduced by timing breastfeeding to avoid peak drug concentrations in milk. Ideally, measurements of drug concentrations in serum and urine of the breastfed infant would help to clarify the unsolved questions. Moreover, long-term studies in exposed children are urgently needed.

KEY POINTS

- Most drugs given to a lactating mother appear in breast milk at approximately maternal plasma levels
- For the drugs discussed in this article, the total daily exposure of the breastfed infant is less than 10% of the therapeutic dose in children
- NSAIDs, paracetamol, corticosteroids, antimalarial agents, and sulfasalazine are compatible with breastfeeding
- Infants breastfed by mothers receiving azathioprine, methotrexate or ciclosporin should be monitored for adverse effects
- Drug exposure can be reduced by timing breastfeeding to avoid peak drug concentrations in milk
- The lack of data on biologic agents in lactating patients with rheumatoid arthritis means that these patients are often not treated with the most effective therapies
- Further studies of the transfer of antirheumatic drugs into breast milk and the resulting consequences are urgently needed

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Acknowledgments
Désirée Lie, University of California, Irvine, CA, is the author of and is solely responsible for the content of the learning objectives, questions and answers of the Medscape-accredited continuing medical education activity associated with this article.

Competing interests
The authors declared they have no competing interests.

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