Maternal medication and breastfeeding: Current recommendations.

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Introduction

The benefits of breastfeeding for infants in the first year of life in developing countries[1] and developed countries[2] are well established. In addition, maternal benefits such as earlier return to pre-pregnant weight,[3] increased child spacing,[4] improved bone re-mineralization postpartum,[5] reduction in hip fractures in the post-menopausal period,[6] reduced risk of ovarian cancer[7] and pre-menopausal breast cancer,[8] are well described. Thus a decision to deny the infant and mother the potential benefits of breast feeding must be carefully considered, and based on the best available evidence.

The average transfer of most medications into human milk is exceedingly low[9] and there are very few instances when breast feeding is absolutely contraindicated. However, there are a number of medications where the available advice in national formularies is limited to manufacturer's cautionary statements to meet the minimum requirement of the licensing authority. Fortunately is research available to inform decisions regarding the use of these medications.

Available Resources

The short list of groups of agents that are commonly quoted as being contraindicated in breastfeeding is Cytotoxic agents, Radioactive compounds, Drugs of Abuse and Ergotamine. But, there are exceptions, additions, cautions and knowledge gaps. The most recent American Academy of Pediatrics (AAP) review, in 2001, has summarised most of the available evidence,[10] but still leaves some areas open to variable interpretation. The AAP review also uses difficult descriptions such as, "Effect unknown but may be of concern" and "Usually compatible with breastfeeding".

There are several other reviews and monographs that provide more detailed analysis and management.[11-13,17,19, 20,21]. The WHO published a document in 2003 that is freely available on the internet[19], which comments specifically on the safety of drugs on the essential drugs list. The advise given is easier to follow than the AAP summmary[10]. In addition, the Medicines Information Centre (MIC), University of Cape Town, has an on-line data base of drugs used in lactation[20]. Both of these resources provide guidelines that are easier to follow than the AAP guidelines and the MIC data base explains the reasons for the levels of concern.

Other particularly useful on-line resources are:
http://www.perinatology.com/exposures/druglist.htm
http://www.medsafe.govt.nz/Profs/PUarticles/lactation.htm

Excretion of drugs in breast milk and subsequent effect in the infant

The milk:plasma (M:P) ratio describes the extent to which a drug is concentrated in breast milk, but the effect of this medication is ultimately determined by the amount of milk that the infant ingests and the therapeutic dose of the drug[9]. Thus, even drugs which are concentrated in breast milk, may be safe if the ultimate dose ingested is sub-therapeutic. If the dose (mg/kg/day) received by the infant (Relative Infant Dose, RID or Exposure Index, EI) is less than 10% of the therapeutic dose then it is safe unless the drug or it's active metabolites accumulate.[13] The RDI is thus directly proportional to the M:P ratio and inversely proportional to the rate of clearance of the drug by the infant[9]. Drugs with low rates of clearance will probably result in higher levels of exposure and drugs with high rates of clearance will result in a low level of exposure, even if the M:P ratio is high. Ito and Koren[9] described this relationship with the following equation: $RDI = [A \times (M:P \text{ ratio}/CL_1)] \times 100$. A = milk intake per Kg per minute, and CL_1 = rate of drug clearance of the infant (ml/kg/minute).

Current Recommendations

Despite the available research quoted, regarding M:P ratios and RDIs, this information is of limited value as milk intake per kg varies from infant to infant and within the same infant with time.

Thus all infants should be monitored for adverse effects that are possible in their mothers, according to the package insert, this is particularly true of substances which have specific side effects such as sulphur drugs and antibiotics that may precipitate haemolysis with G6PD deficiency, and agents which are associated with allergic reactions, such as Quinine.

The following tables summarise medications, according to group, that are contra-indicated, or best avoided during breast feeding. Also included in the table are those agents where concern has been expressed by the AAP, but where sufficient research exists to proceed with breastfeeding (eg; Metoclopramide). Comment about the level of concern, effects and then alternatives is provided where available. Several comprehensive reviews[10,13,17,19,20,21] formed the basis for this data and original source references are only quoted where they provide information not found in, or different to the main reviews consulted. The three most comprehensive data bases and their opinions (status) are shown for comparison.

This summary is not exhaustive and it must be remembered that even where avoidance is suggested, that the risks and benefits of breast feeding need to be weighed up. In addition, there are strategies available to minimise exposure: feed pre dosage and express milk during short courses.

Table 1: Drugs that are generally contraindicated in Breastfeeding[10,19,13,20]

Drug	MIC Status	AAP Status	WHO Status	Reason for concern/effect	Comment	Alternative / Recommendation
Cytotoxics and all other antineoplastics	**C**	**C**	**C**	*The three agents below are mentioned specifically by the AAP.These, and all other Cytotoxics are listed and contraindicated in the WHO list during breast feeding because of potential immune suppression, neutropaenia, carcinogenesis and unknown effect on growth.*		
Cyclophosphamide	**C**	**C**	**C**	Neonatal Neutropaenia reported[17]		***Contra-indicated***
Doxorubicin	**C**	**C**	**C**	Possible immune suppression, carcinogenesis, neutropenia. Unknown side effects on growth. Cardiac toxicity and myelosuppression.M:P 4.4 [21]		***Contra-indicated***
Methotrexate	**C**	**C**	**C**	M:P Ratio <0.1 RID 0.3%. [17] Low weekly doses used for arthritis are probably low risk for infant.[21]		***Mothers being treated with Methotrexate can make informed choice.***
Drugs of Abuse						
Amphetamine	**C**	**C**	**N**	Irritability, poor sleeping pattern, Maternal lactation inhibition.	Concentrated in Breast milk. Detected in neonatal urine.	***Contra-indicated***
Cocaine	**C**	**C**	**N**	Seizures, withdrawal symptoms, Increased risk of sids	*Methadone* used for treatment of addiction is safe for breastfeeding infants at a maternal dose of up to 80mg/day[15] Morphine M:P 2.5	***Contra-indicated*** *Methadone is maternal drug of "choice" only if controlled.* ***Opioids are NOT contraindicated with short-term therapeutic use.***
Heroin/Morphine	**C**	**C**	**N**	Withdrawal symptoms		
Phencyclidine (PCP)	**C**	**C**	**N**	Potent hallucinagen[21]	M:P >10[17]	***Contra-indicated***
Marijuana	**C**	**C**	**N**	May cause developmental delay[16]	Minimal data available	***Contra-indicated***
Alcohol	**AS**	**com**	N	Inhibits milk ejection reflex. Excessive drinking causes lethargy and motor delay in the infant.[21, 11]	M:P 0.9 [38]	***Occasional alcohol permissible, but avoid breastfeeding 1-2 hours after intake if possible.***
Immune Supressants						
Azathioprine	**AS**	N	**C**	Theoretical Immune suppression, neutopaenia.[21]	RID 0.1% [17] No side effects in the 9 reported cases of exposure[13]	*Allow mothers to make informed choice based on reports. Monitor serum levels in mother and blood count in infant.*
Cyclosporin	**C**	**C**	**C**	Theoretical Immune suppression, neutopaenia.[21]	M:P=0.3 RID 0.04%[17] Recent report found levels in milk to be undetectable.[18] But other reports differ[20]	***Contra-indicated until more data available.***
Radioactive Compounds						***All radioactive compounds are contraindicated***
All radioactive compounds	**C**	**C**	**C**	Radioactivity persists in the milk for at least the half-life of the compound – in some cases (^{67}Ga, ^{125}I, ^{131}I) as long as 2 weeks.[10]	Recommendations vary regarding recommendation of duration of cessation of breast feeding.	*Express milk prior to exposure and resume breastfeeding when radioactivity levels are safe. Use agents with negligible radioactivity after the shortest period:* *^{99m}Tc macroaggregates: safe to resume breast feeding after 24 hours[14]* *For other agents, safest practice is to monitor radioactivity in milk after each half life and resume breastfeeding when it is at background levels.*

Key ***C:*** *Contra-indicated,* ***AS****: Avoid if possible and monitor for side-effects,* ***N****: No comment,* ***SEC****: Significant effects reported, suggest caution,* ***UNc****; Unknown effect, but may be of concern,* ***coms****: usually compatible, but monitor for side effects,* ***com:*** *compatible with breast feeding.*

Table 2: Drugs that should be avoided or may require careful infant monitoring.[10,19,13,20]

Drug	MIC Status	AAP Status	WHO Status	Reason for concern/effect	Comment	Recommendation
Antiarrhythmic agents						
Amiodorone	**C**	**UNc**	**N**	Possible hypothyroidism[12,30]	RID 37% [38] Long elimination half-life and high proportion of iodine contained in each dose[12]	***Amiodarone Contra-indicated, if exposure within months of breastfeeding[30]***
Procainamide	**AS**	**com**	**coms**	Concentrated in breast milk. Slowly eliminated from neonates.[11]	M:P 4, RID 5% [17]	***Agents of choice are: Digoxin,Lidocaine,Quinidine***
Disopyramide, Flecanide, Mexiletine,	**AS**	**OK**	**N**	Limited Data[21]		
Antibiotics						
Metronidazole (High Dose)	**AS**	**UNc**	**AS**	In vitro mutagen[21]	M:P = 1, RID 10-20%[21]	***Stop breast feeding x 12h post high dose. Standard doses probably safe[11]***
Chloramphenicol	**C**	**UNc**	**AS**	Possible idiosyncratic marrow suppression – no reported cases[21] M:P 0.5		***Contra-indicated[11]***
Tetracyclines	**AS**	**coms**	**AS**	Potential for staining teeth but negligible amounts in breastmilk – no reported cases[21] M:P 0.6 RID 4-6% [38]		***Avoid, but short courses probably safe.[13]***
Clindamycin, Quinolones, Aminoglycosides	**AS**	**com**	**AS**	These agents are found in breastmilk in very small amounts, and AAP deems breastfeeding to be compatible, but they should be avoided if alternative agents are available.		***Antibiotics that are considered safe[20] are: Cepholsporins,Vancomycin,Macrolides, Penicillins, Trimethoprim***
Sulfamethoxypyridazine	**AS**	**N**	**N**	High concentrations in breast milk. Haemolysis in G6PD def. infant.[11, 21]		***Avoid***
Anticholinergics						
Atropine	**caution**	**com**	**coms**	Possible anticholinergic effects in infant[21]	No reported effects[10]	***Use with caution***
Anticoagulants						
Phenindione	**C**	**SEC**	**N**	Anticoagulant effect in infant.[13]	Phenindione not used in the US RID 15%[17]	***Phenidione Contra-indicated.*** *Wafarin and Heparin are safe.*
Anticonvulsants						
Ethosuxamide	**AS**	**UNc**	**AS**	Poor feeding and sedation in all 3 of these agents.[13]	RID> 10%[13]	*Recommended agents are; Phenytoin (but 1 case report of methaemoglobinaemia), Valproic acid (but individual reports of hepatitis and marrow suppression), Clonazepam. There is insufficient data on the newer agents[26, 27].*
Phenobarbital	**AS**	**SEC**	**coms**			
Primidone	**AS**	**SEC**	**N**			
Carbamazepine	**AS**	**UNc**	**CS**	Previously thought to be safe but recent reports of poor feeding and cholestasis[26] M:P 0.38 RID 2.8 – 7.3% [38]		***Avoid if possible and monitor liver function in neonate.***
Lamotrigine	**AS**	**UNc**	**N**	Potential therapeutic serum concentrations in infant.[26]	M:P 0.6, RID 23-33% No adverse effects in 5 reported infants.[26]	***Avoid if possible*** *Monitor for GI, haematological and dermatological adverse effects.*
Antidepressants						
Lithium	**C**	**SEC**	**AS**	Plasma concentrations in infant may reach 50% of maternal levels and toxicity (apathy, restlessness, vomiting, diarrhoea, weakness) been reported.[37]	Few complications have been identified if mother's plasma levels are kept at 0.5mmol/L 12 hours after ingestion[17].	***Lithium should be avoided****, but if breastfeeding is continued it is essential to monitor maternal serum levels and monitor infant for apathy, irritability, vomiting. Valproic acid is a safer alternative for mania[24].*
Doxepin	**C**	**UNc**	**N**	Several reports of respiratory symptoms hypotonia & sedation.[13,23]	M:P 0.7-1.1 RID 0.8%[17] There are several more suitable alternatives.	***Doxepin is Contraindicated.*** *Recommended Tricyclic antidepressants include Amitriptaline, desipramine, nortryptoline and amoxapine. (RDI 1.5%)[24]*
Fluoxetine	**caution**	**SEC**	**N**	Colic, sedation, irritability, diarrhoea [23]	M:P 0.3-0.5, RID 6-13% [17]	***Avoid Fluoxetine if possible.*** *Recommended Selective Serotonin Reuptake inhibitors are Sertraline and Paroxetine.[23]*

Drug	MIC Status	AAP Status	WHO Status	Reason for concern/effect	Comment	Recommendation
Antihistamines						
Clemastine	**AS**	**SEC**	**N**	One case of irritability, feeding difficulties, drowsiness and hyperexcitability.[27]	M:P 0.25 – 0.5[17]	*Although the other antihistamines are generally considered safe, data is generally lacking. Terfenadine has been associated with irritability[27] and Diphenhydramine is contraindicated by the manufacturer.* ***Agent of choice is Loratidine[28]***
Antihypertensives						
Atenolol Acebutolol	**AS**	**SEC**	**AS**	Hypotension and bradycardia reported[21]	RIDs [23]: Acebutolol: 3.5% Atenolol: 5.7 – 19.2%	***Beta-blockers of choice are Labetolol and Propanolol[21]*** *(RIDs: 0.07& 0.9 respectively)* ***Hydralazine appears to be safe but minimal data is available[21]*** ***Ca-channel blocker of choice is verapamil[21].*** ***ACE inhibitors of choice are Enalapril, Captopril[21].*** ***Central acting agent of choice is methyl dopa[21]***
Alpha-blockers	**AS**	**N**	**N**	Indoramin and Prazosin are both excreted in breastmilk and no safety studies are avialable[31]		
Minoxidil	**AS**	**com**	**N**	Limited data[21]		
Moxonidine	**C**	**N**	**N**	Concentrated in breastmilk[31]		
Reserpine	**AS**	**N**	**C**	Increased secretions[21]		
Clonidine	**AS**	**N**	**N**	May decrease maternal prolactin[21]		
Anti-inflammatories						
Aspirin High Dose	**C/AS**	**SEC**	**N**	1 case of metabolic acidosis [21]	Occasional doses probably safe[21] M:P 0.06 RID 3%[17]	***Avoid salicylates if possible****(due to possible idiosyncratic association with Reye's syndrome)*
Dipyrone (NSAID)	**AS**	**com**	**N**	High concentrations in milk. Potential for agranulocytosis.[33]	One report of cyanosis.[33]	***Safe NSAIDS include:Diclofenac, Ibuprofen, Flurbiprofen,Ketoralac[20]***
Gold Salts	**AS**	**com**	**N**	Potential nephritis& hepatitis 1 study showed higher infant dose than maternal dose.[32]	No actual reported side effects	***Avoid or close monitoring of infant.***
Phenylbutazone Indomethacin	**AS**	**com**	**N**	One case of seizures. Long half life[12]	Minimal excretion in milk[12] Side effects most unlikely.	***Use other NSAIDS if possible***
Antimalarials						
Mefloquine	**C**	**N**	**C**	Lack of data[21]	M:P 0.15 RID 8%[17]	***Chloroquine and Quinine are safe, but allergy to Quinine possible[11]***
Antimycobacterials						
Clofazimine	**AS**	**UNc**	**coms**	Reversible skin discoloration[21]	Minimal Data	***All common antituberculuos drugs (Isoniazid, Rifampicin, pyrazinamide, ethambutol) are compatible with breast feeding as long as infant is monitored for jaundice.[19]***
Dapsone	**AS**	**com**	**coms**	Haemolytic anaemia[21] M:P 0.4 RID 20%[17]	Avoid in Newborns and G6PD deficiency	
Cycloserine	**AS**	**com**	**N**	Comcentrated in breast milk[21]	Insufficient data	
Antithyroid Agents						
Carbimazole	**NC**	**UNc**	**N**	Neonatal Goitre[10]	M:P 1-1.2 RID 3-12%[17]	***Propylthiouracil is a safe alternative[21]***
Antipsychotics						
Clozapine	**C**	**UNc**	**N**	Potential Agranulocytosis.[11]	RDI 1% , no reported side effects[17]	***Avoid Clozapine and Chlorpromazine.*** *No agent is ideal, because of the potential for sedation, but the newer atypical agents, Risperidone and Olanzapine have a better side effect profile in adults, RDIs of 4.3 and 1.6% respectively and small short term studies show no infant side effects. Side effects have also not been present with Haloperidol, but developmental scores are lower[24]*
Chlorpromazine	**AS**	**UNc**	**AS**	Reported to significantly increase sleep apnoea in neonates[24]		

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Table 2: Drugs that should be avoided or may require careful infant monitoring.[10,19,13,20] (Continued)

Drug	MIC Status	AAP Status	WHO Status	Reason for concern/effect	Comment	Recommendation
Anxiolitics						
Diazepam, Alprazolam, Midazolam, Lorazepam	**AS**	**UNc**	**AS**	Long term chronic use causes sedation.[13]	Short term, intermittent use is safe. RIDs vary: 0.7 - 2	***Short term use (1 -2 weeks) is usually safe**, long term daily exposure should be avoided.[24] Short acting agents preferred.*
Diuretics						
Loop diuretics Long acting thiazide diuretics	**AS**	**coms**	**N**	May suppress lactation. Long-acting agents may accumulate.[21]		***Hydrochlorthiazide in low doses is safe although high doses may suppress lactation[21] Acetazolemide is safe.***
Gastrointestinal agents						
Metoclopramide	**com**	**UNc**	**AS**	Increases maternal prolactin. Appears in the breast milk[34] May increase maternal depression and seizures, and precipitate serotonin syndrome in women taking SSRIs.[40]	No side effects seen in infants of mother taking up to 45mg/day[34] RID 4.7 – 11.3%[38]	***Safe for infants and is still the recommended first line galactogogue in healthy mothers,[36] but it is contraindicated in mothers with phaechromocytoma, a history of depression, psychiatric disorders, or seizures[41].*** *Domperidone has less CNS side effects and is an effective galactogogue[39].*
Sulphasalazine Mesalazine	**coms**	**SEC**	**AS**	One case each of diarrhoea reported in the literature in infants of mothers taking this medication.[21]	But studies have shown that insignificant amounts of Sulphasalazine are excreted in breast milk[29](RID 0.3- 0.6)[17] RID 6-10%[17]	***Sulphasalazine is probably safe but infant should be monitored for diarrhoea.***
Hormonal Agents						
Ergotamine (antimigraine doses)	**C**	**SEC**	**AS**	Suppresses lactation. May cause convulsions[21]		***Contra-indicated***
Bromocriptine	**C**	**SEC**	**N**	Suppresses lactation. Maternal strokes, seizures, hypertension and heart attacks reported.[25]	May still have a role suppressing lactation in non breastfeeding women but they must be informed of risks	***Contra-indicated.*** *Mothers who decide to nurse after receiving bromocriptine should probably wait up to one week before breast-feeding because of the long halflife.[21]*
Combined Contraceptive	**AS**	**coms**	**AS**	May inhibit lactation or cause gynaecomastia.[10]		*Oral Contraceptives should not be taken during the first six weeks post partum. Thereafter, the progestogen- only (minipill), Depot-medroxyprogesterone acetate or levonorgestrol implants are preferred methods.[21,11]*
Cyproterone acetate	**C**	**N**	**N**	Concentrated in breast milk[11]		***Contra-indicated***
MAOIs - irreversible	**C**	**N**	**N**	Inhibited catecholamine metabolism		***Contra-indicated[24]***
MAOIs - reversible	**PS**	**N**	**N**		Eg: Moclobamide; M:P = 0.75 RID = 1.1%[20]	***Probably Safe[20]***
Miscellaneous						
Bromide	**AS**	**coms**	**N**	Rash,Weakness[21]		***Avoid***
Iodides and Iodine	**C**	**coms**	**AS**	Systemic, topical and vaginal povidone-iodine in nursing mothers results in elevated milk concentration and thyroid suppression in nursing infants.[21]		***Should not be used***
Theophylline	**caution**	**coms**	**com**	Irritability been described[21]	Significant infant exposure unlikely if maternal serum levels in the normal range[21]	***Keep maternal serum levels in normal range. Monitor infant.***

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