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Adverse Drug Reaction (ADR) Monitoring in TUTH

The Drug Information Unit (DIU) under the Department of Clinical Pharmacology has reported 21 adverse drug reaction cases, mainly from the Medical and Dermatology wards of TUTH during January 2015 to December 2015.

S. No.	Drug Class	Number of Cases
1	Anti-bacterials	6
2	Corticosteroids	5
3	NSAIDs	3
4	Antivirals	2
5	Anticancer drugs	2
6	Anti-coagulants	1
7	Drug Acting on CNS	1
8	Thiazide Diuretics	1
Total		21

"Drug and Therapeutics Letter" is also available in the following website:
<http://www.teachinghospital.org.np/diu.html> <http://www.iom.edu.np/diu.html>

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- Drugs in breastfeeding
- ADR monitoring in TUTH

Drugs in breastfeeding

Introduction

Exclusive breastfeeding for six months, continued alongside complementary food until a minimum of 12 months is recommended by WHO.¹ Most drugs are not of concern during breastfeeding.²⁻⁴ It is important to be able to give accurate advice on the safety of drugs so that breastfeeding is promoted whenever possible.⁵

In addition, most lactating women take few medicines and only occasionally. Even though virtually all drugs are transferred into breast milk to some extent, the amount of drug is usually small and unlikely to cause an adverse effect on the baby.⁵ Thus

it is generally not necessary to suspend breastfeeding because of the mother's medication. If ongoing medication use is necessary, only a few drugs warrant the cessation of breast-feeding. However, given the vulnerability of infants, vigilance is required.

Factors affecting concentration of a drug in milk.

Maternal Plasma concentration

Drugs enter milk primarily by passive diffusion. There is a good concordance between the time-course of maternal plasma drug concentration and drug concentration in milk. The factors responsible are as follows.

Maternal plasma concentration is affected by the drug's distribution into different tissues. A high volume of distribution will contribute to a lower maternal plasma concentration and a subsequent lower concentration in milk.

Table: Examples of drugs contraindicated in breastfeeding⁵

Drug	Comment
Amiodarone	Long half-life, iodine-containing molecule, and may affect thyroid function in infant
Antineoplastics	Leukopenia, bone marrow suppression
Gold salts	Rash, nephritis, haematological abnormalities
Lithium	Breastfeeding only feasible with rigorous monitoring
Radiopharmaceuticals	Contact obstetric information service
Retinoids (oral)	Potential for serious adverse effects

Maternal plasma protein binding

Free unbound drug diffuses readily while highly protein-bound drugs like ibuprofen or warfarin (both 99% protein bound) are unable to diffuse in significant amounts.⁶

Size of the drug molecule

Most drug molecules, including alcohol, nicotine and caffeine, are small enough to enter milk. Exceptions are drugs with high molecular weights such as heparins and insulin.⁵

Degree of ionisation

Drugs cross membranes in an unionised form. Milk is generally slightly more acidic (pH 7.2) than the mother's plasma (pH 7.4) so it attracts weak organic bases such as oxycodone and codeine.⁷ Such drugs become ionised and 'trapped' in the milk.

Lipid solubility

Lipid-soluble drugs such as citalopram⁸ may get co-secreted by dissolution in the fat droplets of milk.² It would not be an indication to change therapy if citalopram has been effective, but infant drowsiness should be monitored.

Maternal pharmacogenomics

A growing understanding of the influence of pharmacogenomics is well exemplified with codeine which is variably metabolised to morphine by the cytochrome P450 (CYP) 2D6 enzyme. Repeated codeine doses in ultra rapid metabolisers produce significant amounts of morphine. Rapid transfer from maternal plasma to the milk may result in central nervous system depression and potentially infant death.⁹ Codeine should be avoided during breastfeeding.¹⁰

Factors affecting the risk of adverse effects on the baby

Timing of the dose

Feeding the baby just before the mother

takes a drug with short half-life results in the baby receiving the lowest possible drug concentration.

Toxicity

Premature babies and neonates have a lower capacity to metabolise and excrete drugs.² In addition, for babies who may already have been exposed to a drug in-utero just before delivery, further exposure via breast milk will augment the existing drug concentration.

Some drugs are inappropriately regarded as unsafe. Metronidazole, despite unfounded fears of carcinogenicity and mutagenicity, is safe in breastfeeding for short-term use.¹¹ Valproate is regarded as safe, especially in monotherapy when the risk of infant sedation is low.¹¹ Monitoring the infant for liver and platelet changes may be advisable.¹²

Oral bioavailability

Omeprazole (usually enteric coated formulation) and gentamicin (intravenous), even if present in breast milk may be degraded or destroyed in infant gut.⁵

Volume of breast milk

The amount of milk a baby receives varies. The estimated intake by an exclusively breastfed baby is 150 mL/kg/day. However, if the breast is being offered only as a comfort to an older baby, for example at night, the volume ingested is likely to be small.

Relative infant dose

The relative infant dose is the dose received via breast milk relative to the mother's dose. It is expressed as a percentage. A relative dose of 10% or above is the notional level of concern,⁶ but this is rare.

Age of infant

A review found that most adverse effects of drugs in breast milk occurred in newborns under two months and rarely in those older than six months.¹³

Drugs used to stimulate milk production

Domperidone and metoclopramide are galactogogues and have both been used off-label to stimulate prolactin and enhance milk supply. However, these drugs do not have high evidence of efficacy for this indication.^{11,14} Correct advice and more frequent breastfeeding can enhance milk secretion.

Practice points for prescribing in breastfeeding

- If a drug is needed, prescribe it at the lowest effective dose. Temporarily suspend breastfeeding (and express milk) for potentially toxic drugs. Reinstatement of a drug will be determined by its half-life.
- Select alternative routes or products to minimise systemic exposure in the mother. For example fibre laxative chosen over stimulant laxative
- Choose drugs with a relatively short half-life, such as sertraline rather than fluoxetine, to minimize drug exposure in milk.
- Advise the mother to feed the infant before taking her medicine so that the drug concentration in milk will be at its lowest. This advice does not apply to drugs with a long half-life.

Advice on social drugs

Advise mothers to delay a glass of alcohol until after a feed and wait for two hours before the next feed to minimise infant exposure. Smoking, including passive smoking, has been associated with sudden infant death syndrome. Nicotine replacement therapy (short acting) is preferable to smoking. High maternal intake of caffeine is associated with irritability and poor sleep patterns in the infant.⁵

Breastfeeding in the context of illicit drug use is likely to be problematic. Women should be encouraged to stop using cannabis and avoid exposure of the baby to second-hand smoke.

Conclusion

Most commonly used drugs are relatively safe for breastfed babies. The dose received via milk is generally small and much less than the known safe doses of the drugs used in neonates and infants. Further, most lactating women take few medications and often only occasionally. However various factors affecting drug concentration in milk need to be considered. In most cases, correct advice and reassurance may suffice, but some drugs will be contraindicated.

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