

Q&A 286.3

## Oral antiplatelet agents—are they safe in breastfeeding?

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### Background

There are five oral antiplatelet agents licensed in the UK: aspirin, dipyridamole, clopidogrel, prasugrel, and ticagrelor (1). In adults, depending on the indication, antiplatelet drugs may be prescribed as monotherapy or used alongside other antiplatelet drugs or anticoagulants (1). In children, aspirin and dipyridamole have limited uses (2).

There are only limited data available for the excretion of oral antiplatelet agents into breast milk. Therefore, an assessment of risk in breastfeeding mothers can be made by taking account of the potential adverse effect profile, and the pharmacological action and pharmacokinetics of each drug, as outlined in Table 1 (3, 4).

Aspirin, clopidogrel and prasugrel bind irreversibly to platelets producing a prolonged anti-aggregant effect for the remainder of their 7–10 day lifespan (4). Recovery of normal platelet function occurs at a rate consistent with platelet turnover. Dipyridamole promotes a moderate endogenous anti-aggregant effect lasting about 24 hours. Ticagrelor reversibly interacts with platelets and the maximum effect on inhibition of platelet aggregation is maintained for 2–8 hours post dose (4).

Table 1: Pharmacokinetics and pharmacological action of oral anti-platelet agents (3, 4, 13)

Antiplatelet	Action	Bioavailability	Half life (hours)	Protein binding
Aspirin low dose	Irreversible COX 1 inhibitor	80–100%	2–3 (active metabolite)	88–93%
Dipyridamole	Reversibly increases the intraplatelet levels of cAMP and adenosine	37–66%	2–3 (parent molecule)	91–99%
Clopidogrel	Irreversible adenosine diphosphate receptor antagonist	>50%	6 (parent molecule) 0.5–0.7 (active metabolite)	98%
Prasugrel	Irreversible adenosine diphosphate receptor antagonist	>79%	7–8 (active metabolite)	98%
Ticagrelor	Reversible indirect adenosine diphosphate receptor antagonist	36%	7 (parent molecule) 9 (active metabolite)	>99%

### Answer

#### Aspirin

Aspirin is rapidly metabolised into its main active metabolite, salicylic acid, in the maternal plasma. Much of the evidence relating to the excretion of salicylic acid into breast milk relates to maternal usage of aspirin at analgesic or anti-inflammatory doses, but there is no evidence relating to mothers taking low dose aspirin as an antiplatelet agent.

The molecular weight of salicylic acid is small enough to expect it to pass into breast milk. However, salicylic acid is highly protein bound and almost completely ionized at a serum pH of 7.4,

therefore only very small amounts are free to pass into breast milk (5). Also, as the pKa of salicylic acid is 3.46 it would not be expected to accumulate in milk, which is slightly more acidic (pH 6.8–7.2) than plasma (5). There is a significant variation however in the amount of salicylic acid reported to pass into the breast milk with analgesic doses. (6).

Several case reports have described serious adverse effects in infants exposed to aspirin via breast milk in mothers taking analgesic or anti-inflammatory doses including metabolic acidosis (7), thrombocytopenia, fever, anorexia and petechiae (8), and haemolysis in a G6PD deficient infant (9). However, the case report describing metabolic acidosis could not rule out direct administration of aspirin to the infant (7). In contrast, a prospective follow-up to detect adverse reactions in 15 breastfed infants exposed to maternal medication did not find any adverse effects, although aspirin doses were unspecified (10). However, no reports describing adverse effects in infants of mothers taking low dose aspirin as an antiplatelet agent could be identified.

Aspirin has been definitively associated with Reye's syndrome when administered to children with fever. Reye's syndrome is a disorder characterised by acute encephalopathy and fatty degeneration of the liver. It occurs almost exclusively in young children although cases have been seen in patients over the age of 12. Many factors may be involved in its aetiology but it typically occurs after a viral infection such as chickenpox or influenza and may be precipitated by a chemical trigger (11). A definitive dose related relationship between aspirin and Reye's syndrome has not been established (12) and it is unknown whether the small amounts present in breast milk following an antiplatelet dose would be clinically significant. To minimize the risk of developing Reye's syndrome, breastfeeding should be withheld if the infant develops a fever. In some cases, it may be also be clinically appropriate to withhold the aspirin for short periods, in order to avoid disrupting breastfeeding.

### **Dipyridamole**

There are no published studies relating to dipyridamole and breast milk. The Summary of Product Characteristics for Persantin® (dipyridamole) tablets states that it is excreted into human milk at levels approximately 6% of the plasma concentration (13). However, this statement cannot be substantiated.

Only small amounts of dipyridamole would be expected to pass into breast milk since oral absorption is poor due to first pass effect, and protein binding is high (13). There are no published reports of adverse effects in infants exposed to dipyridamole via breast milk.

### **Clopidogrel**

There are no published reports relating to clopidogrel in human breast milk or any reports describing adverse events in breastfed infants.

Clopidogrel is a pro-drug which is converted into both active and inactive metabolites which are highly protein bound. The clopidogrel molecule is small enough to pass into breast milk although the pharmacokinetics indicate that the amount excreted is likely to be minimal (14).

### **Prasugrel and Ticagrelor**

There are no published reports relating to prasugrel or ticagrelor in human breast milk, or any reports describing adverse events in breastfed infants

Prasugrel is a pro-drug which is converted into both active and inactive metabolites (3). Ticagrelor does not require hepatic biotransformation but is metabolised to an equipotent active metabolite (4). The molecular weights and half-lives suggest that both drugs would be excreted into breast milk, but because both drugs are highly protein bound this would limit excretion (3). In addition, ticagrelor has very poor oral bioavailability, limiting its availability to the breastfed infant (3).

## Summary

- ◆ Limited data and pharmacokinetics indicate that low dose aspirin and dipyridamole pass into breast milk in small amounts, but there is not enough information to accurately establish the milk/plasma ratio.
- ◆ There is no information regarding excretion of clopidogrel, prasugrel and ticagrelor into breast milk but the amount is likely to be very small due to high protein binding and also possibly due to the irreversible binding to platelets in the case of clopidogrel and prasugrel.
- ◆ There have been no adverse reports described in infants exposed to any of these antiplatelets via breast milk. However, as there are no studies or reports describing safe use in infants exposed via breast milk, they should be used with caution. Infant monitoring of adverse effects described with therapeutic doses in children should be undertaken, especially signs of bruising and bleeding, which may be prolonged (7–10 days) in the case of irreversible antiplatelet agents. Other possible adverse effects include tachycardia, hypersensitivity reactions such as rash, urticaria, dyspnoea, severe bronchospasm, angioedema, increased bleeding during or after surgery, and thrombocytopenia (2).
- ◆ It is unknown whether the small amounts of aspirin present in breast milk following an antiplatelet dose could cause Reye's syndrome in a breastfed infant. To minimize the risk, breastfeeding should be withheld if the infant develops a fever, or consider temporarily discontinuing the aspirin if clinically justified.

## Limitations

- Evidence of the secretion of aspirin into breast milk, and its safety in breastfed infants, is limited to relatively small studies with limited numbers of mothers and infants. Evidence for long-term safety is lacking.
- There are no reports regarding the excretion of clopidogrel, prasugrel, ticagrelor or dipyridamole that could be substantiated.
- The information relates to full-term and healthy infants. If the infant is pre-term, of low birth weight or has other concomitant pathology or medical problems, then specialist advice should be sought. *Contact the UK Drugs in Lactation Advisory Service (UKDILAS) provided jointly by the Trent and West Midlands Medicines Information Services (0116 258 6491 or 0121 424 7298).*

## References

1. Joint Formulary Committee. *British National Formulary* (online) London: BMJ Group and Pharmaceutical Press. Available from [www.evidence.nhs.uk/formulary/bnf/current](http://www.evidence.nhs.uk/formulary/bnf/current). Accessed 9 October 2015.
2. Paediatric Formulary Committee. *BNF for Children* (online) London: BMJ Group, Pharmaceutical Press, and RCPCH Publications. Available from [www.evidence.nhs.uk/formulary/bnfc/current](http://www.evidence.nhs.uk/formulary/bnfc/current). Accessed 9 October 2015.
3. Thomas Hale. Hale Publishing. Medications and Mothers Milk. Available from [www.medsmilk.com/menu.html](http://www.medsmilk.com/menu.html). Accessed 9 October 2015.
4. DRUGDEX® System: Rohit Romesh Arora (Ed DRUGDEX® System (electronic version). Thomson Micromedex, Greenwood Village, Colorado, USA. Available from [www.thomsonhc.com](http://www.thomsonhc.com). Accessed 9 October 2015.
5. Erickson SH, Oppenheim GL. Aspirin in breast milk. *J Fam Pract* 1979;8:189–90
6. Jamali F, Keshavarz E. Salicylate excretion in breast milk. *Int J Pharm* 1981;8:285–90
7. Clark JH, Wilson WG. A 16-day-old breast-fed infant with metabolic acidosis caused by salicylate. *Clin Pediatr (Phila)* 1981;20: 53–4.
8. Terragna A, Spirito L. Porpora trombocitopenica in lattante dopo somministrazione di acido acetilsalicilico alla nutrice. [Thrombocytopenic purpura in an infant after administration of acetylsalicylic acid to the wet-nurse. *Minerva Pediatr* 1967; 19: 613–6.
9. Harley JD, Robin H. "Late" neonatal jaundice in infants with glucose-6-phosphate dehydrogenase-

- deficient erythrocytes. *Australas Ann Med* 1962; 11:148–55.
10. Ito S, Blajchman A, Stephenson M, Eliopoulos C et al. Prospective follow-up of adverse reactions in breast-fed infants exposed to maternal medication. *Am J Obstet Gynecol* 1993; 168:1393–9
  11. Sweetman SC (ed), *Martindale: The Complete Drug Reference*. [online] London: Pharmaceutical Press . Available from [www.medicinescomplete.com](http://www.medicinescomplete.com) . Accessed 6 November 2015.
  12. Glasgow JF. Reye's syndrome—The case for a causal link with aspirin. *Drug Saf* 2006;29:1111-1121.
  13. Summary of Product Characteristics—Persantin (dipyridamole) Tablets 100 mg. Available from [www.emc.medicines.org.uk](http://www.emc.medicines.org.uk). Accessed 6 November 2015 (date of revision of the text February 2015).
  14. Summary of Product Characteristics—Plavix (clopidogrel) 75mg and 300mg film coated tablets. Available from [www.emc.medicines.org.uk](http://www.emc.medicines.org.uk). Accessed 6 November 2015 (date of revision of the text 21 May 2015).

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## Search strategy

- Embase and Medline (Standard UKDILAS Search Patterns)
- In-house UKDILAS database
- Medications and Mothers' Milk Online (Medilact): various monographs
- 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>. Various monographs
- Manufacturers (eMC)