

Q&amp;A 318.3

## Is topical glyceryl trinitrate for anal fissure compatible with breastfeeding

Prepared by UK Medicines Information (UKMi) pharmacists for NHS healthcare professionals

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### Background

Anal fissure is a tear in the squamous epithelium lining the distal anal canal near the mucocutaneous junction (1,2). Causes of secondary anal fissure include constipation, inflammatory bowel disease, sexually transmitted disease, local or systemic malignancy, trauma or chemotherapy and the third trimester of pregnancy (1,2). It also occurs in up to 15% of women following childbirth (3,4).

### Answer

#### General

In the UK, guidance on the medical management of anal fissure has been issued by the NHS Clinical Knowledge Summaries (NHS CKS) and the Association of Coloproctology of Great Britain and Ireland (ACPGBI) (1,5). Current advice from the NHS CKS is that topical glyceryl trinitrate (GTN) should be offered to adults with primary anal fissure if symptoms have been present for more than one week without improvement and they have been informed of associated benefits and harms. Treatment should be for up to 8 weeks or until the fissure is fully healed (1).

An evidence based review for the use of non surgical therapy for anal fissures was published by the Cochrane Collaboration in 2012 (2), Conclusions from an analysis of the results of 75 randomised controlled trials (n=5031) were that GTN therapy was significantly better than placebo in healing anal fissure (48.9% vs. 35.5%,  $p < 0.0009$ ) but late recurrence of fissure was common (in the range of 50% of those initially cured) (2).

#### Topical glyceryl trinitrate with breastfeeding

Glyceryl trinitrate (GTN) acts as a nitric oxide donor and is thought to aid healing by relaxing the internal anal sphincter resulting in a reduction of anal pressure and an improvement in anoderm blood flow (6).

The manufacturer advises against the use of topical GTN whilst breastfeeding on the basis of a lack of evidence and potential harmful effects on a breastfed infant. It is thought that some systemic absorption does occur during use. In six healthy subjects, the average bioavailability of GTN applied to the anal canal as a 0.2% ointment was approximately 50% of the 0.75 mg dose (7).

Topical use of GTN for anal fissures by nursing mothers appears to have no adverse effects on their breastfed infants. Sublingual and intravenous GTN have not been studied during breastfeeding. The only published study of topical GTN use with breastfeeding is in a short report of 40 nursing mothers who used GTN ointment (dosage not specified) topically for the treatment of postpartum anal fissures for durations ranging from 1 to 12 months of intermittent use. All but 9 of the women reported maternal side effects from therapy, primarily headache, but also dizziness or light headedness. None of the mothers reported any side effects in their breastfed infants. The authors concluded that breastfeeding mothers can be reassured that the amount of GTN transferred into breast milk is unlikely to cause any symptoms in their babies and that, if the mother tolerates the side effects herself, she can safely use topical GTN while continuing to breastfeed (8).

The following estimation suggests that the infant's exposure will be very low. The normal dose applied is stated to be about 375 mg of 0.2% ointment, equivalent to approximately 1.5 mg GTN (7). In kinetic studies, cutaneous application of 8–16 mg resulted in peak plasma levels of 1 nanogram/ml (9). Accepted milk intake is about 150 ml/kg/day; a 6-week infant will weigh around 4–4.5 kg, corresponding to an intake of 600–700 mL milk daily. Even if milk levels were greater than plasma levels and the infant breastfed at times of peak plasma concentrations, the amount ingested by the infant will be no more than a few micrograms daily. GTN has limited bioavailability, therefore the

amount systemically absorbed will be less still. This amount is considered to be clinically negligible (10).

It is further suggested that the mother breastfeeds immediately before application of the GTN ointment and avoids breastfeeding for 1 to 2 hours afterwards to minimise exposure of the infant to GTN via milk. The mother should also be advised to wash her hands to remove any ointment before touching the infant (10).

## Summary

- ◆ GTN ointment is commonly used to treat postpartum anal fissure and is compatible with breastfeeding on the basis of pharmacokinetic data with only limited evidence of safe use in breastfed infants.
- ◆ Mothers should be advised to breastfeed the infant immediately before application of the ointment to minimise exposure and to try to avoid breastfeeding for 1–2 hours after use.
- ◆ Mothers should be advised to wash hands immediately after use to avoid topical contact with infant.

## Limitations

- Evidence of the secretion of glyceryl trinitrate into breast milk is not available, and evidence relating to its safety in breastfed infants after topical administration to the mother is limited to one small study.
- Evidence for long-term safety is also not available
- The information relates to full term and healthy infants. Evidence in preterm infants is lacking. If the infant is pre-term, of low birth weight or has other concomitant pathology or medical problems, then specialist advice should be sought as this answer may not apply. *Contact the UK Drugs in Lactation Advisory Service (UKDILAS) provided by the Trent and West Midlands Medicines Information Services.*

## References

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## Quality Assurance

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### Search strategy

- Embase (search strategy: [ exp fissure in ano.DE./ + (exp nitroglycerin.DE. OR exp isosorbide dinitrate.DE. OR exp nitrates.DE. OR (isosorbide AND mononitrate))]. Limited to Human and English language.
- Medline (search strategy: [exp fissure in ano.DE. + [exp nitroglycerin.DE. OR exp isosorbide dinitrate.DE. OR exp nitrates.DE. OR (isosorbide AND mononitrate))]. Limited to Human and English language
- UK Drugs in Lactation Advisory Service – in-house data-base
- Medline and Embase: Standard UKDILAS search pattern found at <http://www.ukmi.nhs.uk/activities/specialistServices/default.asp?pageRef=2>  
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