

METOCLOPRAMIDE (Commentary)**Use of metoclopramide for suspected gastroesophageal reflux**

Reflux is extremely common in young babies. In one recent survey two thirds of all four month old children seen in a well baby clinic were reported to be regurgitating at least once a day, and there has been pressure to 'medicalise' what is often a benign and self-limiting problem for the last twenty years. Cisapride was widely used for some years until the manufacturers took this drug off the market because the prolongation of the QT interval that it caused occasionally precipitated an arrhythmia. Metoclopramide started to be widely prescribed soon after this (Clark *et al.*, 2006) and many think that its current widespread use (Barron *et al.*, 2007; Malcolm *et al.*, 2008) can not be justified (Kjoshoo *et al.*, 2007) especially as there is little evidence that it provides most babies with any meaningful symptomatic relief (Hibbs and Lorch, 2006; Wheatley and Kennedy, 2009). There have been no controlled trials of its use in the preterm neonate. Indeed, there is no good evidence that any anti-reflux medication reduces the frequency of apnea in the preterm baby (Kimball and Carlton, 2001), and continued uncertainty as to how severe the symptoms have to be for the condition to be treated as a 'disease' (Dhillon and Ewer, 2004; Vandenplas *et al.*, 2005). Feed thickening (as outlined in the monograph on carob seed flour) is, at the moment, one of the few strategies for which there is any – albeit modest – evidence of benefit.

- Kimball AI, Carlton DP. Gastroesophageal reflux medications in the treatment of apnea in premature infants. *J Pediatr* 2001;**138**:355–60.
- Dhillon AS, Ewer AK. Diagnosis and management of gastro-oesophageal reflux in preterm infants in neonatal intensive care units. *Acta Paediatr* 2004;**93**:88–93.
- Vandenplas Y, Salvatore S, Hauser B. The diagnosis and management of gastro-oesophageal reflux in infants. *Early Hum Dev* 2005;**81**:1011–24.
- Clark RH, Bloom BT, Spitzer AR, *et al.* Reported medication use in the neonatal intensive care unit: data from a large national data set. *Pediatrics* 2006;**117**:1979–87.
- Hibbs AM, Lorch SA. Metoclopramide for the treatment of gastroesophageal reflux disease in infants: systematic review. *Pediatrics* 2006;**118**:746–52. [SR]
- Martin RJ, Hibbs AM. Diagnosing gastroesophageal reflux in preterm infants. [Commentary] *Pediatrics* 2006;**118**:793–4.
- Khoshoo V, Edel D, Thompson A, *et al.* Are we overprescribing antireflux medications for infants with regurgitations? *Pediatrics* 2007;**120**:946–9. (See also 2008;**121**:1070–1.)
- Barron JA, Tan H, Spalding J, *et al.* Proton pump inhibitor utilisation patterns in infants. *J Pediatr Gastroenterol Nutr* 2007;**45**:421–7.
- Malcolm WF, Gantz M, Nartub RJ, *et al.* Use of medications for gastroesophageal reflux at discharge among extremely low birth weight infants. *Pediatrics* 2008;**121**:22–7.
- Slocum C, Arko M, Di FJ, *et al.* Apnea, bradycardia and desaturation in preterm infants before and after feeding. *J Perinatol* 2009;**29**:209–12.
- Wheatley E, Kennedy KA. Cross-over trial of treatment for bradycardia attributed to gastroesophageal reflux in preterm infants. *J Pediatr* 2009;**155**:516–21. [RCT] (See also 494–5.)

How should nausea and vomiting be managed in infancy?

While nausea and vomiting in infancy do not often call for drug treatment, and the main focus should be on sustaining fluid balance as outlined in the monograph about oral rehydration solutions (q.v.), there are occasions when medication does have a role. Metoclopramide has been quite widely used for this purpose despite all the caveats that have been voiced about such use, but we now know that, at least in the management of post-operative vomiting, ondansetron (q.v.) seems to be a better option. There is also better evidence for the use of ondansetron to control severe symptoms in gastroenteritis.

- Kathirvel S, Shende D, Madan R. Comparison of anti-emetic effects of ondansetron, metoclopramide or a combination of both in children undergoing surgery for strabismus. *Eur J Anaesthesiol* 1999;**16**:761–5. [RCT]
- Bolton CM, Myles PS, Carlin JB, *et al.* Randomized, double-blind study comparing the efficacy of moderate-dose metoclopramide and ondansetron for the prophylactic control of postoperative vomiting in children after tonsillectomy. *Br J Anaesth* 2000;**99**:699–703. [RCT]

Drug use to stimulate lactation

A lot of interest was shown in the use of drugs to help lactation over a period of nearly twenty years, stimulated by an understanding of the impact that the hormone prolactin has on milk production, once free from the inhibiting influence of the high oestrogen and placental lactogen levels seen during pregnancy. Several drugs known to stimulate prolactin production were studied to see if they could be of help to women who were finding it difficult to breast feeding their baby (metoclopramide being the most popular), but this approach to the problem has now generally gone out of favour. Many felt that such an approach seldom did much to help, and more felt that it was merely 'medicalising' yet another aspect of childbirth. Anderson and Valdés published an excellent recent overview of all the available evidence in 2007, and Nicky Wesson reviewed the evidence for herbal remedies in 2009. What comes over again and again is that if help, support and advice *is* available then drugs make little difference (Sakha and Behbhan, 2008), and McInness and Chambers provided a good overview of the work that has been done to identify the best way to provide such support in 2008.

- Anderson PO, Valdés V. Increasing breast milk supply. *Clin Pharm* 1993;**12**:479–80.

- Hill PD, Aldag JC, Chatterton RT. The effect of sequential and simultaneous breast pumping on milk volume and prolactin levels: a pilot study. *J Hum Lact* 1996;**12**:193–9.
- Emery MM. Galactagogues: drugs to induce lactation. *J Hum Lact* 1996;**12**:55–7.
- Chatterton RT, Hill PD, Aldag JC, *et al.* Relation of plasma oxytocin and prolactin concentrations to milk production in mothers of preterm infants: influence of stress. *J Clin Endocrinol Metab* 2000;**85**:3661–8.
- Royal College of Midwives. *Successful breastfeeding*. 3rd ed. Edinburgh: Churchill Livingstone, 2002.
- Hale TW, Berens P. *Clinical therapy in breastfeeding patients*. 2nd ed. Emarillo Texas: Pharmasoft Publishing, 2002.
- Anderson PO, Valdés V. A critical review of pharmaceutical galactagogues. *Breastfeeding Medicine* 2007;**2**:229–42.
- Sakha K, Behbahan AG. Training for perfect breastfeeding or metoclopramide: which one can promote lactation in nursing mothers. *Breastfeeding Medicine* 2008;**3**:120–3.
- McInnes RJ, Chambers JA. Supporting breastfeeding mothers: qualitative synthesis. *J Adv Nurs* 2008;**62**:407–27.
- Wesson N. Breast milk production and the role of galactagogues. *MIDIRS Midwifery Digest* 2009;**19**:400–7.

Domperidone: Domperidone is a dopamine-receptor agonist used to relieve nausea and vomiting and, because of its effect on prolactin excretion it has, like metoclopramide, sometimes been given to women to facilitate lactation. The only rigorous study of this strategy to date has been the small randomised controlled trial reported by da Silva *et al.* in 2001 involving just 16 mothers who were having trouble with lactation following preterm birth. The dose most commonly used to improve lactation is 10 or 20 mg by mouth three or even four times a day. Excretion into breast milk is negligible (Hofmeyr *et al.*, 1985; Wan *et al.*, 2008)

- O'Meara A, Mott M. Domperidone as an antiemetic in pediatric oncology. *Cancer Chemother Pharmacol* 1981;**6**:147–9.
- Hofmeyr GJ, van Iddekinge B. Domperidone and lactation. *Lancet* 1983 ;i:647.
- Hofmeyr GJ, van Iddekinge B, Blott JA. Domperidone: excretion in breast milk and effect on puerperal prolactin levels. *Br J Obstet Gynaecol* 1985;**92**:141–4.
- Petraglia F, De Leo V, Sardelli S, *et al.* Domperidone in defective and insufficient lactation. *Eur J Obstet Gynecol Reprod Biol* 1985;**19**:281–7.
- da Silva OP, Knoppert DC, Angelini MM, *et al.* Effect of domperidone on milk production in mothers of premature newborns: a randomized, double-blind, placebo-controlled trial *CMAJ* 2001;**164**:17–21. [RCT]
- Wan E W-X, Davey K, Page-Sharp M, *et al.* Dose-effect study of domperidone as a galactagogue in preterm mothers with insufficient milk supply, and its transfer into milk. *Br J Clin Pharmacol* 2008;**66**:283–9. [RCT]

Metoclopramide: There is no doubt that this drug can stimulate milk production by increasing maternal prolactin levels (Lewis *et al.*, 1980; Kauppila *et al.*, 1981). While a dose of just 5 mg by mouth three times a day is seldom of much help, a 10 mg dose three times a day is often of measurable benefit, and a 15 mg dose three times a day can sometimes be even more helpful. The most encouraging reports were Kauppila's study of 37 women in 1983, Gupta's study of 32 women in 1985, and Ehrenkranz's study of 23 women with preterm babies in the same year. However a trial of the use of the drug in 28 women delivered failed to produce any evidence of benefit (Hansen *et al.*, 2005). Treatment can cause the woman to experience abdominal cramp and diarrhoea so the lowest effective dose should always be used. More seriously the mother's milk supply often falls again when treatment stops and, since there is said to be an increased risk of depression in women taking this drug for more than a month treatment should be tapered gradually once an effect is achieved and stopped if there is no response after a week. Metoclopramide crosses the placenta readily (Arvela *et al.*, 1983) but the amount ingested by the baby if this drug is used to stimulate lactation is too small to be of significance (Ertl *et al.*, 1991). Metoclopramide is still occasionally used to promote lactation in some countries like America where domperidone is not commercially available, but the latter is generally perceived to be the better alternative because it produces fewer dystonic problems and seems less likely to cause depression.

- Sousa PLR. Metoclopramide and breast feeding. *BMJ* 1975;**1**:512.
- Guzman V, Toscano G, Canales ES, *et al.* Improvement of defective lactation by using oral metoclopramide. *Acta Obstet Gynaecol Scand* 1979;**58**:53–5.
- Lewis PJ, Devenish C, Kahn C. Controlled trial of metoclopramide in the initiation of breast-feeding. *Br J Clin Pharmacol* 1980;**9**:217–9. [RCT]
- Kauppila A, Kivinen S, Ylikorkala O. A dose response relation between improved lactation and metoclopramide. *Lancet* 1981;i:1175–7.
- Kauppila A, Kivinen S, Ylikorkala O. Metoclopramide increases prolactin release and milk secretion in puerperium without stimulating the secretion of thyrotropin and thyroid hormones. *J Clin Endocrinol Metab* 1981;**52**:436–9.
- Arvela P, Joupila R, Kauppila A, *et al.* Placental transfer and hormonal effects of metoclopramide. *Eur J Clin Pharmacol* 1983;**24**:345–8.
- Pelkonen O, Arvela P, Kauppila A, *et al.* Metoclopramide in breast milk and newborn. [Abstract] *Acta Physiol Scand* 1982 (suppl 502):62.
- de Gezelle H, Ooghe W, Thiery M, *et al.* Metoclopramide and breast milk. *Eur J Obstet Gynecol Reprod Biol* 1983;**15**:31–6.
- Kauppila A, Arvela P, Koivisto M, *et al.* Metoclopramide and breast feeding: transfer into breast milk and the newborn. *Eur J Clin Pharmacol* 1983;**25**:819–23.
- Kauppila A, Anunto P, Kivinen S, *et al.* Metoclopramide and breast-feeding: efficacy and anterior pituitary responses of the mother and child. *Eur J Obstet Gynecol Reprod Biol* 1985;**19**:19–22.
- Gupta AP, Gupta PK. Metoclopramide as a lactagogue. *Clin Pediatr* 1985;**24**:269–72.
- Ehrenkranz RA, Ackerman BA. Metoclopramide effect on faltering milk production by mothers of premature infants. *Pediatrics* 1986;**78**:614–20.
- Ertl T, Sulyok E, Ezer E, *et al.* The influence of metoclopramide on the composition of human breast milk. *Acta Paediatr Hung* 1991;**31**:415–22.
- Budd SC, Erdman SH, Long DM, *et al.* Improved lactation with metoclopramide. *Clin Pediatr* 1993;**32**:53–7.

Toppare MF, Laleli Y, Senses DA, *et al.* Metoclopramide for breast milk production. *Nutr Res* 1994;**14**:1019–23.
Hansen WF, McAndrews S, Harris K, *et al.* Metoclopramide effect on breastfeeding the preterm infant: a randomized trial. *Obstet Gynecol* 2005;**105**:383–9. [RCT]
Sakha K, Benbahan AG. Training for perfect breastfeeding or metoclopramide: which one can promote lactation in nursing mothers? *Breastfeed Med* 2008;**3**:120–3.

Oxytocin: Because the “let down” reflex, which is primed by oxytocin release from the posterior pituitary, is known to be essential for successful breast feeding, a number of studies of its clinical use to support lactation were undertaken soon after it became possible to give the drug as a nasal spray. Three small trials in the early 1980s suggested that oxytocin could help stimulate early lactation in healthy mothers, while another found oxytocin of value in mothers who could not put their baby to the breast immediately after birth. However, these studies are now of limited clinical relevance because the preparations that were used in those studies are no longer commercially available, access to the breast was quite severely restricted in these studies, and all the babies were also offered supplementary dextrose feeds. In addition, a more recent trial by Fewtrell *et al.* in 2006 (which used a 100 µl dose) failed to find any evidence to support the use of oxytocin in this way.

Ruis H, Rolland R, Doesburg W, *et al.* Oxytocin enhances onset of lactation among mothers delivering prematurely. *BMJ* 1981;**283**:340–2. [RCT]
Fewtrell MS, Loh KL, Meek J, *et al.* Randomised, double blind trial of oxytocin nasal spray in mothers expressing milk for preterm infants. *Arch Dis Child* 2006;**91**:F169–74. [RCT]

Sulpiride: Ylikorkala *et al.* reported in 1982 and 1984 that a 50 mg dose of sulpiride three times a day increased maternal prolactin levels, but it only seemed to have a modest impact on milk production. This approach does not seem to have received further study.

Aono T, Shioji T, Aki T, *et al.* Augmentation of puerperal lactation by oral administration of sulpiride. *J Clin Endocrin Metabol* 1979;**48**:478–82.
Aono T, Aski T, Koike K, *et al.* Effect of sulpiride on poor puerperal lactation. *Am J Obstet Gynecol* 1982;**143**:927–32.
Ylikorkala O, Kaullila A, Knivinen S, *et al.* Sulpiride improves inadequate lactation. *BMJ* 1982;**285**:249–51.
Ylikorkala O, Kaullila A, Knivinen S, *et al.* Treatment of inadequate lactation with oral sulpiride and buccal oxytocin. *Obstet Gynecol* 1984;**63**:57–60.

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