SPANZA Advisory on Tramadol - Use of Tramadol during breastfeeding and in the Neonate

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Society for Paediatric Anaesthesia in New Zealand and Australia

Background

On 20th April 2017 the FDA issued a drug safety communication recommending against the use of codeine and tramadol medicines in breastfeeding mothers due to possible harm to their infants.

The communication included: "A strengthened "warning" to mothers that breastfeeding is not recommended when taking codeine or tramadol medicines due to the risk of serious adverse reactions in breastfed infants. These can include excess sleepiness, difficulty breastfeeding, or serious breathing problems that could result in death."

SPANZA response and recommendations

Tramadol is used in parenteral (IV) and oral forms as an analgesic in breastfeeding mothers internationally [1]. It is used in children (off label under the age of 12 years) in many hospitals internationally including tertiary paediatric settings [1]. The tramadol parent drug and its M1 metabolite (formed by the liver enzyme CYP2D6) are both active and provide analgesia by different pathways. The tramadol parent drug causes the adverse effect of sedation (and does not suppress breathing) and the M1 metabolite has opioid effects and may cause both sedation and respiratory depression (opioid induced ventilatory impairment).

Tramadol has had widespread use following major surgery in Neonatal Intensive Care Units. There are a small number of trials documenting clinical use for analgesia in neonates [2, 3] and neonatal pharmacokinetics [4-7]. Conclusions about the safety of tramadol in the newborn are limited by the small size of these data.

The amount of tramadol excreted into maternal breast milk is known to be a small percentage of the mother's dose (less than 2.5%). In a trial of 75 breastfeeding mothers who were given tramadol 100 mg six hourly on day 2-4 after caesarean section [8], the estimated absolute infant exposure was 112 µg/kg/day for tramadol (2.24% relative to the mother) and 30 µg/kg/day for the active M1 metabolite (0.64% relative to the mother). The M1 metabolite exposure is lower because it is water soluble (fat soluble agents are more readily excreted in breast milk). Newborns whose mothers received tramadol had similar neurological function outcome measures as the control newborns.

The target analgesic concentration of tramadol for postoperative analgesia is 300 mcg/L [4]. This is achieved by an infusion of about 100 mcg/kg/h which equates to 600 mcg/kg 6 hourly [4]. Clinically used doses [1] are 2 to 3 fold higher than this: 100-200 mcg/kg/h [2] or 1-2 mg/kg 6 hourly [3]. The dose a newborn receives from breast milk is therefore less than 5% of the dose a neonate receives for analgesia.

A term neonate's ability to convert tramadol by the liver enzyme CYP2D6 to M1 is 50% compared to an adult [7] and this results in a limited mu-opioid receptor M1 mediated analgesic effect at this age, and even less so in preterm neonates. The current pharmacokinetic observations are that the CYP2D6 enzyme is immature in the newborn. Consequently the development of ultra(fast) metabolism leading to elevated M1 concentrations and adverse effect is not clinically relevant in this age group and polymorphism of the enzyme only becomes relevant beyond term age and in later life [7, 9]. A newborn's capacity to renally excrete M1 is also reduced, by approximately 30% compared to adults [10]. Due to the slow maturation of the CYP2D6 enzyme, the plasma concentrations of M1 are low until infants are 3 months old, wherein renal elimination, which is still immature, becomes relevant and higher plasma concentrations are predicted [11, 12]. However, given the small amount ingested in breast milk, both newborns and older infants are able to effectively eliminate both the parent drug and its metabolite.

Tramadol is not codeine. Codeine has little analgesic activity and it is the metabolite morphine that is active and provides analgesia. Morphine is produced through CYP2D6 activity. Both inactive codeine and morphine (as codeine's metabolite) are excreted in breast milk. Morphine is similarly fat soluble to codeine and tramadol, while M1 is more water soluble. The FDA review of the medical literature of data regarding codeine use during breastfeeding found numerous cases of excess sedation and respiratory depression in breastfed infants[13]: referencing[14] and including one death (published twice [15, 16]). The mother in this case took repeated doses of paracetamol combined with codeine for several days. She was an ultrarapid metaboliser and her plasma concentration of morphine was 4 times the upper limit of normal. Her newborn developed drowsiness on day 7 and died on day 13 of life with morphine plasma concentration that was 35 times the upper limit of reported in breast fed neonates, and 3.5 times the upper limit that causes respiratory depression in neonates. A literature review of tramadol use during breastfeeding did not

reveal any similar cases of adverse events. While both Tramadol and its M1 metabolite are present in breast milk, there is no evidence that it has the same risks associated with ultra-rapid metabolism as codeine suggested by the FDA statement [13].

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Importantly, full agonist opioids such as oxycodone and codeine are reported to have high rates of sedative effect in both the mothers using it postpartum and central nervous system depression in their breastfed neonates[17]. If this contraindication is adopted for tramadol, it is likely to lead to increased full agonist opioid prescription for peripartum analgesia, with possible increased risk to the breastfed newborn. More comparative data is required to determine the relative safety of the various opioid analgesics available for prescription in this setting.

The panel's conclusions regarding tramadol in breast feeding mothers are

1. Maternal tramadol use results in small amounts of active parent drug tramadol and even smaller amounts of the active metabolite (M1) being ingested by the breastfed newborn.
2. The newborn's liver is able to effectively metabolise this low dose of tramadol.
3. The newborn's kidneys are able to eliminate the low dose of M1 metabolite.
4. The concentrations of tramadol and M1 metabolite are less than 5% of the neonates plasma concentrations after an analgesic dose or infusion is administered and thus sedation and suppression of the breastfed newborn's breathing is very unlikely.

Recommendations

1. Tramadol should remain a part of the multimodal analgesic regime in breast feeding mothers postpartum
2. Tramadol is safer in this setting than other opioids (including codeine) that are also excreted in the breast milk.
3. The alternatives to tramadol, for example oxycodone and morphine, are more likely than Tramadol and its M1 metabolite to cause sedation and respiratory depression (opioid induced ventilatory impairment) in the newborn.
4. The warning against use in breast feeding mothers applied to codeine (whose active metabolite formed by CYP2D6 is morphine) should not be applied to tramadol.
5. More comparative data is required to determine the relative safety of the various opioid analgesics available for prescription in this setting.

A SPANZA review panel have liaised and include:

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Other relevant documents

http://www.spanza.org.au/images/17_05_SPANZA_Advisory_on_Tramadol_31_May_2017.pdf SPANZA's statement on the use of Tramadol in children having tonsillectomy under the age of 18 years in May 2017 in response to the new FDA contraindication

FDA Drug Safety Communication: Use of Codeine and Tramadol Products in Breastfeeding Women - Questions and Answers. (April 2017) (https://www.fda.gov/Drugs/DrugSafety/ucm118113.htm)

FDA Drug Safety Communication: FDA restricts use of prescription codeine pain and cough medicines and tramadol pain medicines in children; recommends against use in breastfeeding women (April 20th 2017). (https://www.fda.gov/Drugs/DrugSafety/ucm549679.htm)

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