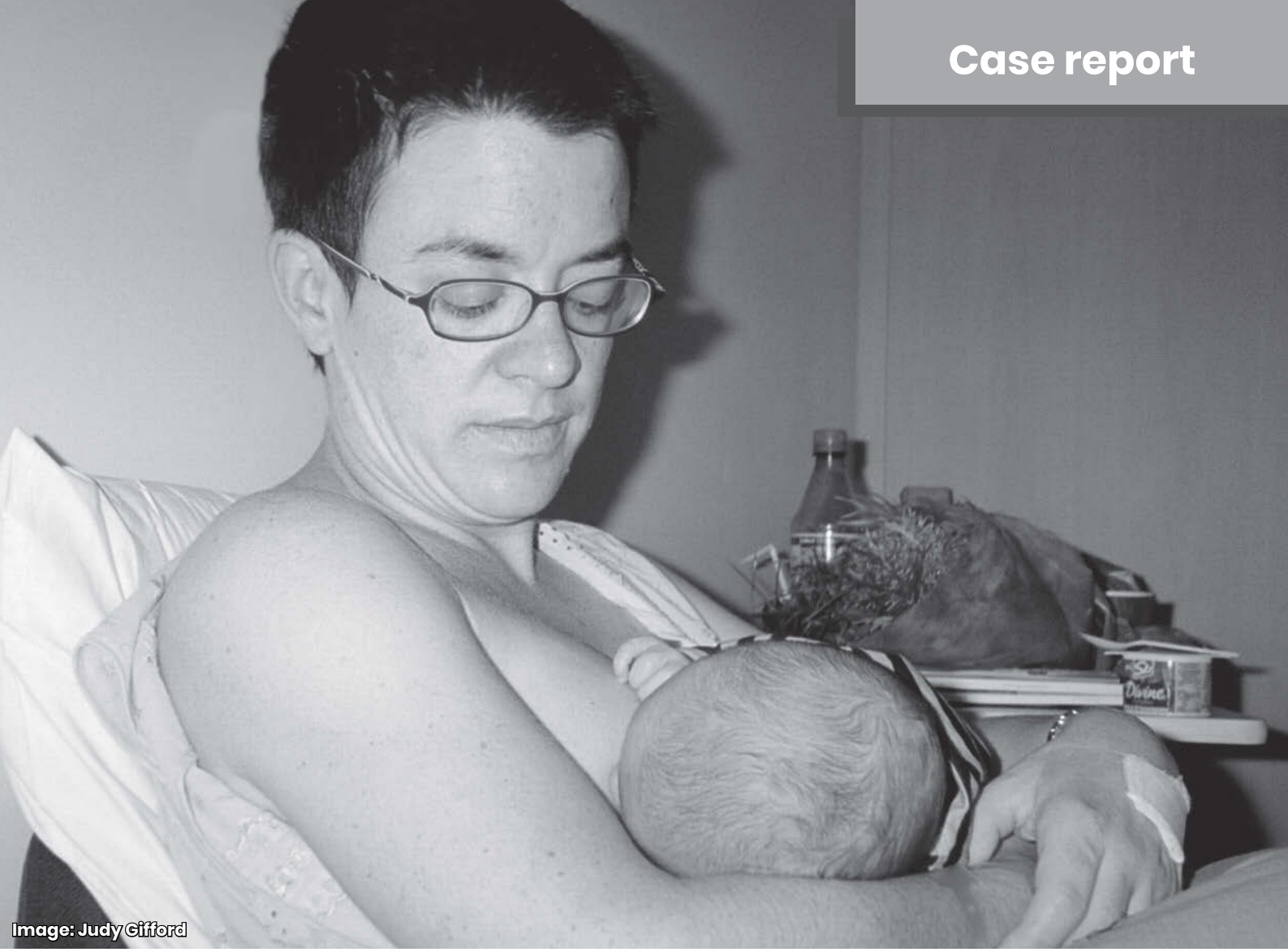

Image: Judy Gifford

Is maternal therapeutic opioid use instigating misdiagnosis in breastfed infants? A case report

Hilai Ahmadzai, Andrew Crowe, Lisa BG Tee

ABSTRACT

Despite the known risks associated with opioid use during breastfeeding, their place in therapy is established as part of a multimodal approach to treatment of pain in the early postpartum period. Opioids may be prescribed for post-caesarean analgesia without adequate patient education, resulting in adverse drug events in breastfed infants. We report the case of an exclusively breastfed 6-day-old infant who presented with symptoms of progressive drowsiness, somnolence and inability to feed. Maternal medication use was discounted as a potential causative factor and it was not explored further, despite the mother taking a long-acting opioid at the time. A series of invasive investigative tests were carried out and the infant was commenced on intravenous antibiotics for suspected sepsis. All test results were negative for infections and no causes for the symptoms. The infant was discharged 3 days later with a formal diagnosis of a '*probable viral infection*'. A lack of understanding by healthcare professionals of the impact of maternal medication use (particularly drugs with known risks) on breastfed infants can result in infant ADE, inappropriate prescribing, stress and anxiety for new parents and a lost opportunity to contribute to lactation-related medicines information.

Keywords: *breastfeeding, neonatal adverse drug events, opioids, maternal medication use, case report*

***Breastfeeding Review* 2020; 28(2), 27–32**

INTRODUCTION

The aim of this case report is to highlight and raise awareness of the adverse effects of maternal medication use, particularly of opioid analgesics, on breastfed infants which can be a great source of anxiety for new parents and have an economic impact on our already stretched health resources. We also aim to highlight the importance of patient education and medication counselling to breastfeeding mothers to increase their awareness of possible adverse drug events (ADE) in their breastfed infant due to the transfer of maternal medicines via breastmilk, and to encourage investigation and reporting of perceived breastfeeding related ADE.

Written parental consent was obtained for the publication of this case report in addition to ethics approval from the Curtin University Human Research Ethics Committee (HR110/2012).

Case presentation

A female baby was born at 38+6 weeks' gestation (birth weight 2.6 kg) by caesarean section on the background of oligohydramnios (low amniotic fluid) and intrauterine growth retardation. The APGAR scores at birth were 9 and 9 at 1 and 5 minutes respectively. The baby had no post-birth complications and was discharged home on day 5. Lactation was fully established on day 3. The mother was healthy with no prior medical conditions and no history of medication use other than pregnancy multivitamins. For postpartum analgesia, the mother was prescribed diclofenac 50 mg, a non-steroidal anti-inflammatory drug three times daily and Di-Gesic® (containing paracetamol/dextropropoxyphene) 650 mg/65 mg (equivalent to two tablets) 6-hourly. The mother took 13 doses of the analgesics as follows: Day 2: 3 doses | Day 3: 3 doses | Day 4: 3 doses | Day 5: 3 doses| Day 6: 1 dose.

On day 6 postpartum, the mother noticed her exclusively breastfed infant to be drowsy, falling asleep during feeds and unresponsive to stimuli, including pain (pinching of the toes). The infant was rushed to the local paediatric hospital for assessment. Although initial observations such as body temperature, oxygen saturation, heart rate and blood pressure were unremarkable, investigative tests such as full blood picture, blood cultures, lumbar puncture and urine microscopy culture and sensitivities were ordered. The infant was commenced on intravenous fluids for hydration, and empirical antibiotics (benzylpenicillin and cefotaxime) to cover for sepsis and meningitis.

Despite the initial blood test results not showing any abnormalities, the infant was closely monitored while waiting for the microscopy and culture results. Over the ensuing 24 hours, the infant's vital observations remained unremarkable. The mother had ceased taking Di-Gesic® (last dose being on the morning of day 6 postpartum) and at this stage was taking only paracetamol for pain relief. In addition to intravenous hydration, breastfeeding was continued, and the baby was observed to be more alert with noticeable improvements in feeding. The investigative tests returned normal results and did not show any abnormalities or infections in the infant as shown in table 1. Vital observations also remained unremarkable during the entire admission. Antibiotics were ceased after 36 hours and the infant was discharged home after 3 days of hospitalisation with a formal diagnosis of a 'probable viral infection'.

The mother stated that she volunteered information about her Di-Gesic® use to the doctors on two occasions in the emergency ward and again in the inpatient ward as she was aware of the notion that foods and medicines taken by a mother can affect her breastfed infant. However, she was assured by junior and senior paediatric doctors that Di-Gesic® was unlikely to have caused the baby's symptoms, with the junior doctor declaring *'if the obstetrician prescribed it, it is safe*'.

A retrospective review of the infant's medical notes from this admission demonstrated that:

- there was no documentation of maternal medication use at any stage
- there was no mention of maternal Di-Gesic® use in the infant's medical record
- potential drug exposure was not considered as a causative factor for the presenting symptoms of the infant
- vital observations on admission were unremarkable
- differential diagnosis on admission was sepsis/ meningitis.

Dextropropoxyphene, a constituent of Di-Gesic® (which also contains paracetamol as an active ingredient) is a synthetic weak opioid analgesic that was first manufactured in the 1950s. Due to safety concerns, dextropropoxyphene containing products have been withdrawn from various countries in Europe, the USA and New Zealand. Despite this, cases of serious harm due to this drug are still emerging (Delcher, Chen, Wang, Slavova, & Goldberger, 2017). In Australia, any dextropropoxyphene containing medicines including Di-Gesic® were supposed to be withdrawn from 1 March 2012, but the drug manufacturer sought a review in the Administrative Appeals Tribunal which ruled in 2013 that the drugs could be sold under strict conditions (Buckley & Faunce, 2013). One condition was that doctors were required to complete a prescriber confirmation form when prescribing this medication to a patient, with copies of this form provided to the dispensing pharmacist and the patient. The completion

Table 1. Laboratory test results of the infant on admission, and day 3 blood culture results.

Test	Result	Normal range
Inflammatory marker		
C-reactive protein	<5 mg/L	<15 mg/L
Full blood picture		
Haemoglobin	174 g/L	135–195 g/L
White cell count	12.10 × 10^9/L	5–25 × 10^9/L
Platelet count	472 × 10^9/L	150–400 × 10^9/L
Neutrophils absolute	3.02 × 10^9/L	3–18 × 10^9/L
Lymphocytes absolute	7.02 × 10^9/L	2–10 × 10^9/L
Monocytes absolute	1.81 × 10^9/L	0.2–2.2 × 10^9/L
Eosinophils absolute	0.24 × 10^9/L	0.0–0.5 × 10^9/L
Urea and electrolytes		
Sodium — plasma	139 mmol/L	132–147 mmol/L
Potassium — plasma	5.1 mmol/L	3.5–6.2 mmol/L
Bicarbonate — plasma	19 mmol/L	17–28 mmol/L
Urea — plasma	2.4 mmol/L	2–8 mmol/L
Creatinine — plasma	37 µmol/L	22–93 µmol/L
Cerebrospinal fluid		
Glucose	2.6 mmol/L	2.7–4.4 mmol/L
Protein	1.04 g/L	0.3–1.10 g/L
Microbiology results		
CSF culture	No growth	
Blood culture	No growth	
Nucleic acid detection tests		
Enterovirus RNA	Not detected	
Neisseria meningitidis DNA	Not detected	
Human parechovirus	Not detected	

of this form was meant to serve as an endorsement that the prescriber had considered alternatives and confirmed that there were none suitable, that they had considered recent changes to the patient's clinical presentation and biochemical markers, and that they had discussed with their patient the appropriate use of the dextropropoxyphene product including the risks of overdose (Buckley & Faunce, 2013). At the time of this incident in November 2016, dextropropoxyphene was available strictly under these conditions.

The mother stated that on the morning of her discharge from the hospital, the obstetrician in charge informed her that she would receive analgesics for pain but further details such as drug names or regimens were not discussed. The mother stated that she could not recall being visited by a pharmacist and consequently did not get to speak to one at all during the course of her admission or on discharge from the maternity hospital. The limited medication counselling the mother received was part of the discharge facilitation process from the nurse on duty who reiterated the dosage instructions written on the labels of the dispensed medicines which included Di-Gesic® and diclofenac. However, no additional education or written medicines information were offered.

DISCUSSION

Correct management of pain in the postpartum period is essential to minimise the risk of adverse outcomes to the mother and baby. Inadequate treatment of pain can lead to the development of anxiety and depression, which can impact on a woman's physical and psychological well-being, as well as her ability to provide care for her baby (Bisson, Newell, & Laxton, 2019). Maternal opioids used for management of pain are known to cause adverse effects such as respiratory depression and death in breastfed infants (Hendrickson & McKeown, 2012; Soussan et al., 2014). Dextropropoxyphene hydrochloride, prescribed to the mother of this infant, is a centrally acting, synthetic opioid analgesic structurally related to methadone (Rigourd, Amirouche, Tasseau, Kintz, & Serreau, 2008). The half-life of dextropropoxyphene is 6 to 12 hours but the half-life of its metabolite, norpropoxyphene is 30 to 36 hours (Drugs and Lactation Database (LactMed), 2006). Due to its long half-life, norpropoxyphene is known to accumulate in breastmilk and cause adverse effects, especially in the first 2 months of an infant's life, due to the underdeveloped infant excretory and metabolic systems (Koyyalagunta, 2007; Kunka, Venkataramanan, Stern, & Ladik, 1984). Breastfeeding-associated infant adverse drug reactions reported to the French Pharmacovigilance Database centre attributed 11 of the 174 adverse drug reactions reported between 1985 and 2011 to maternal dextropropoxyphene use (Soussan et al., 2014). Furthermore, several other cases of full-term breastfed infants with unexplained episodes of apnoea, bradycardia or cyanosis during the first week of life have been attributed to maternal oral dextropropoxyphene (Naumburg & Meny, 1988; Rigourd et al., 2008).

At the time of this incident the evidence linking dextropropoxyphene to adverse effects in breastfed infants was sufficient to cause concern and warrant investigation of symptoms of toxicity in this infant. Despite this, frontline staff unreservedly dismissed maternal medication use as a potential causative factor and assumed its safety because it was prescribed by an obstetrician. Although no opioid is considered absolutely safe in breastfeeding, particularly with extended use, Di-Gesic® seems to be a very questionable choice. Furthermore, the mother was ill-informed about the possible side effects of her medicines as she was not provided with adequate medicines education (written or oral) upon discharge from the hospital, as required by legislation at the time.

Since all opioids have been shown to carry the risk of causing infant adverse effects, many regulatory bodies such as the Royal Australian and New Zealand College of Obstetrics and Gynaecologists recommend that the use of opioids be limited to the shortest duration possible (Ito, 2018; van den Anker, 2012). In recent times, substantial evidence has emerged linking codeine, a commonly used weak opioid, with infant mortality. As a result, codeine is no longer recommended in lactation due to the risk of accumulation and infant mortality, particularly in CYP2D6 ultra-rapid metabolisers (Koren, Cairns, Chitayat, Gaedigk, & Leeder, 2006; Willmann, Edginton, Coboeken, Ahr, & Lippert, 2009). Since the recommendations against codeine use in breastfeeding, tramadol and oxycodone are increasingly being utilised as the opioids of choice. While tramadol is considered safer in breastfeeding, it is a weak analgesic and may not provide adequate analgesia, necessitating the use of more potent agents such as oxycodone (Palmer, Anderson, Linscott, Paech, & Allegaert, 2018). Evidence suggests that oxycodone is not much safer than codeine in causing infant adverse drug reactions, with some studies showing higher CNS depressant adverse effects compared to codeine (Ito, 2018; Lam et al., 2012; Timm, 2013). A recent study of calls to US poisons centres found that 88% of serious effects such as lethargy, cyanosis, respiratory depression and drowsiness in breastfeeding neonates was associated with maternal opioid use (Beauchamp, Hendrickson, Horowitz, & Spyker, 2019).

Due to the overwhelming evidence of maternal opioid use causing ADE in breastfed infants, it is recommended that postoperative pain management for caesarean section should be multimodal in approach, with non-opioids such as paracetamol and non-steroidal anti-inflammatories to be the mainstay of treatment and opioids to be reserved for breakthrough pain only (Sutton & Carvalho, 2017). Despite this, global evidence suggests that opioids are being prescribed postpartum, often in quantities greater than needed and possibly without adequate maternal education (Badreldin, Grobman, Chang, & Yee, 2018; Osmundson et al., 2017). While currently such studies have not been conducted in Australia, a lack of comparable data in this case does not rule out the occurrence of such events.

It is acknowledged that establishing a causal relationship between a clinical presentation in an infant and their exposure to medications via breastmilk is inherently difficult, particularly when the signs and symptoms are not obvious or definitive. Most available breastfeeding-related safety data is based upon small observational studies with short-term follow up of less than a year. Long-term studies or randomised controlled trials are generally not conducted in breastfeeding babies due to ethical considerations. This lack of large-scale and quality breastfeeding-related safety data may possibly lead to busy healthcare professionals being reluctant to commit resources to investigate and report such events to regulatory bodies, which in turn prevents the generation of more data. This is apparent from research conducted by our team (unpublished data) which

shows that breastfeeding-related adverse events reported to the Therapeutics Goods Administration are infrequent and incomplete. This case report is a perfect example of this phenomenon, where maternal concerns regarding transfer of dextropropoxyphene to the infant via breastmilk were not taken seriously and were dismissed without appropriate investigation. Based on the reported interactions of the mother with doctors, it appears that unfamiliarity and a lack of knowledge about dextropropoxyphene were contributing factors, as demonstrated by the doctor's remarks '*if the obstetrician prescribed it, it is safe*'. Perhaps, consideration should be given to the use of urine toxicology as part of the investigation of breastfed infants who present with non-specific symptoms and where a history of maternal medication use is established. Liquid chromatography techniques are commonly used to reliably detect and quantify the presence of opioids, including norpropoxyphene, in urine samples (Milone, 2012; Puet et al., 2013).

The parents of this infant, in retrospect, expressed disappointment that they were not provided any information about the mother's prescribed medicines, especially the well-known side effects of Di-Gesic®. They reported having grave concerns for the health and safety of their newborn daughter when they witnessed her '*floppy body*' and her '*unresponsiveness to the pinching of her toes*'. The parents described spending 3 days in hospital and seeing their baby undergo a lumbar puncture as '*heart breaking and excruciatingly traumatic*' for what they believed could have '*possibly been a preventable cause*' but one that they '*will never find out for sure as breastmilk testing did not occur*'. The emotional pain undergone by the parents was described as '*far worse than the physical pain of the caesarean section*' by the mother, who thereafter refused to take analgesics other than occasional paracetamol for the pain due to the fear of passing it to her baby through breastmilk. While they reported being grateful for the care that their daughter received at the hospital, they expressed displeasure at the dismissal of their concerns by the doctors and what they perceived as '*not being heard*' during a time that they described as '*the most traumatic experience for a new parent*'.

CONCLUSION

The risk of infections and sepsis in a newborn infant is not only high, but of great concern due to the associated morbidity and mortality and should be thoroughly considered upon presentation of any signs and symptoms. However, in an exclusively breastfed infant, other factors such as maternal medication use (especially when high-risk drugs with known adverse effects such as opioids are involved) should also be considered as an alternative differential diagnosis. It is therefore imperative that health professionals such as doctors, pharmacists and nurses are aware of the impact of maternal medication use and its potential effect in breastfed infants, particularly in the first 2 months of life and ensure that it is not only managed but also investigated appropriately.

DECLARATION

The authors of this manuscript wish to declare that there are no conflicts of interest. No financial assistance or funding was received from any sources towards this article.

REFERENCES

Badreldin, N., Grobman, W. A., Chang, K. T., & Yee, L. M. (2018). Opioid prescribing patterns among postpartum women. *American Journal of Obstetrics and Gynecology, 219*(1), 103.e1–103.e8. https://doi.org/10.1016/j.ajog.2018.04.003

Beauchamp, G. A., Hendrickson, R. G., Horowitz, B. Z., & Spyker, D. A. (2019). Exposures through breast milk: An analysis of exposure and information calls to U.S. Poison Centers, 2001–2017. *Breastfeeding Medicine*, *14*(7), 508–512. https://doi.org/10.1089/bfm.2019.0075

Bisson, D. L., Newell, S. D., & Laxton, C. (2019). Antenatal and postnatal analgesia: Scientific impact paper No. 59. *British Journal of Obstetrics and Gynaecology, 126*(4), e114–e124. https://doi.org/10.1111/1471-0528.15510

Buckley, N. A., & Faunce, T. A. (2013). Trials and tribulations in the removal of dextropropoxyphene from the Australian Register of Therapeutic Goods. *Medical Journal of Australia, 199*(4), 257–260. https://doi.org/10.5694/mja13.10040

Delcher, C., Chen, G., Wang, Y., Slavova, S., & Goldberger, B. A. (2017). Fatal poisonings involving propoxyphene before and after voluntary withdrawal from the United States' market: An analysis from the state of Florida. *Forensic Science International, 280*, 228–232. https://doi.org/10.1016/j.forsciint.2017.10.008

Drugs and Lactation Database (LactMed). (2006). *Propoxyphene*. Retrieved October 28th, 2018 from https://www.ncbi.nlm.nih.gov/books/NBK501250/

Hendrickson, R. G., & McKeown, N. J. (2012). Is maternal opioid use hazardous to breast-fed infants? *Clinical Toxicology (Philadelphia, Pa.), 50*(1), 1–14. https://doi.org/10.3109/15563650.2011.635147

Ito, S. (2018). Opioids in breast milk: Pharmacokinetic principles and clinical implications. *Journal of Clinical Pharmacology, 58 Suppl 10*, S151–s163. https://doi.org/10.1002/jcph.1113

Koren, G., Cairns, J., Chitayat, D., Gaedigk, A., & Leeder, S. J. (2006). Pharmacogenetics of morphine poisoning in a breastfed neonate of a codeine-prescribed mother. *Lancet, 368*(9536), 704. https://doi.org/10.1016/s0140-6736(06)69255-6

Koyyalagunta, D. (2011). Opioid analgesics. In S. D. Waldman (Ed.), *Pain management* (2nd ed.). Philadelphia, PA; Elsevier.

Kunka, R. L., Venkataramanan, R., Stern, R. M., & Ladik, C. F. (1984). Excretion of propoxyphene and norpropoxyphene in breast milk. *Clinical Pharmacology and Therapeutics, 35*(5), 675–680.

Lam, J., Kelly, L., Ciszkowski, C., Landsmeer, M. L., Nauta, M., Carleton, B. C., ... Koren, G. (2012). Central nervous system depression of neonates breastfed by mothers receiving oxycodone for postpartum analgesia. *Journal of Pediatrics, 160*(1), 33–37. e32. https://doi.org/10.1016/j.jpeds.2011.06.050

Milone, M. C. (2012). Laboratory testing for prescription opioids. *Journal of Medical Toxicology, 8*(4), 408–416. https://doi.org/10.1007/s13181-012-0274-7

Naumburg, E. G., & Meny, R. G. (1988). Breast milk opioids and neonatal apnea. *American Journal of Diseases in Childhood, 142*(1), 11–12.

Osmundson, S. S., Schornack, L. A., Grasch, J. L., Zuckerwise, L. C., Young, J. L., & Richardson, M. G. (2017). Postdischarge opioid use after cesarean delivery. *Obstetrics and Gynecology, 130*(1), 36–41. https://doi.org/10.1097/aog.0000000000002095

Palmer, G. M., Anderson, B. J., Linscott, D. K., Paech, M. J., & Allegaert, K. (2018). Tramadol, breast feeding and safety in the newborn. *Archives of Disease in Childhood, 103*(12), 1110–1113. https://doi.org/10.1136/archdischild-2017-313786

Puet, B., DePriest, A., Knight, J., Heltsley, R., Black, D. L., Caplan, Y. H., & Cone, E. J. (2013). Urine drug testing of chronic pain patients. V. Prevalence of propoxyphene following its withdrawal from the United States market. *Journal of Analytical Toxicology, 37*(1), 1–4. https://doi.org/10.1093/jat/bks083

Rigourd, V., Amirouche, A., Tasseau, A., Kintz, P., & Serreau, R. (2008). Retrospective diagnosis of an adverse drug reaction in a breastfed neonate: Liquid chromatography-tandem mass spectrometry quantification of dextropropoxyphene and norpropoxyphene in newborn and maternal hair. *Journal of Analytical Toxicology, 32*(9), 787–789.

Soussan, C., Gouraud, A., Portolan, G., Jean-Pastor, M. J., Pecriaux, C., Montastruc, J. L., ... Lacroix, I. (2014). Drug-induced adverse reactions via breastfeeding: A descriptive study in the French Pharmacovigilance Database. *European Journal Clinical Pharmacology, 70*(11), 1361–1366. https://doi.org/10.1007/s00228-014-1738-2

Sutton, C. D., & Carvalho, B. (2017). Optimal pain management after cesarean delivery. *Anesthesiology Clinics, 35*(1), 107–124. https://doi.org/10.1016/j.anclin.2016.09.010

Timm, N. L. (2013). Maternal use of oxycodone resulting in opioid intoxication in her breastfed neonate. *Journal of Pediatrics, 162*(2), 421–422. https://doi.org/10.1016/j.jpeds.2012.08.047

van den Anker, J. N. (2012). Is it safe to use opioids for obstetric pain while breastfeeding? *Journal of Pediatrics, 160*(1), 4–6. https://doi.org/10.1016/j.jpeds.2011.08.066

Willmann, S., Edginton, A. N., Coboeken, K., Ahr, G., & Lippert, J. (2009). Risk to the breast-fed neonate from codeine treatment to the mother: A quantitative mechanistic modeling study. *Clinical Pharmacology and Therapeutics, 86*(6), 634–643. https://doi.org/10.1038/clpt.2009.151

AUTHORS

Hilai Ahmadzai
Curtin University
School of Pharmacy and Biomedical Sciences
Bentley Campus
Bentley WA 6102
E: hilai.ahmadzai@postgrad.curtin.edu.au

Dr Andrew Crowe
BSc(Hons) (Veterinary Biology) PhD (Physiology and Public Health)
School of Pharmacy and Biomedical Sciences
Curtin University
Building 306; Bentley Campus
Bentley WA 6102
E: A.P.Crowe@curtin.edu.au
P: +61 8 9266 3423

Associate Professor Lisa BG Tee
BSc(Hons)(Pharmacology) PhD(Clinical Pharmacology)
School of Pharmacy and Biomedical Sciences
Curtin University
Building 306; Bentley Campus
Bentley WA 6102
E: L.Tee@curtin.edu.au
P: +61 8 9266 2526