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► To cite this version:

Karel Allegaert, Kenneth F. Ilett, Gideon Koren. Tramadol withdrawal in a neonate: only one of the clinical presentations to be anticipated.... European Journal of Clinical Pharmacology, 2009, 65 (6), pp.643-644. 10.1007/s00228-009-0635-6 . hal-00534949

HAL Id: hal-00534949

<https://hal.science/hal-00534949>

Submitted on 11 Nov 2010

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Tramadol withdrawal in a neonate: only one of the clinical presentations to be anticipated...

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Received: 10 January 2009 / Accepted: 10 February 2009 / Published online: 4 March 2009
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Dear editor,

We read the case report on tramadol withdrawal recently published in this journal with great interest. The authors described a full-term neonate who developed clinical signs of opioid-related withdrawal on the second day of life after being exposed to high dose (200–400 mg/day) maternal tramadol intake throughout pregnancy. Symptom control with tinktura opii was achieved, and treatment was tapered over 2 weeks [1]. The authors hereby confirmed that tramadol, a moderately potent opioid, can also result in neonatal withdrawal, similar to observations after maternal codeine intake. However, a single case observation does not represent the interindividual variability in clinical symptoms. We therefore felt it appropriate to draw the attention of the reader to recently reported observations on the interindividual variability in the pharmacokinetics and

pharmacodynamics of moderately potent opioids such as tramadol and codeine in perinatal life [2–6].

Firstly, interindividual metabolic elimination clearance of tramadol in neonates can only to a limited extent (54%) be explained by the postmenstrual age alone [2]. More recently, it was documented that cytochrome P450 (CYP) 2D6 polymorphisms explain the interindividual variability observed in neonatal metabolic clearance [3]. This means that metabolic clearance capacity through *O*-demethyl tramadol in part depends on age and on CYP2D6 polymorphisms: a preterm neonate will display phenotypic low CYP2D6 activity, while in term neonates and beyond, CYP2D6 activity score is also a relevant contributor of phenotypic metabolic clearance. It is to be anticipated that this will have an impact on the extent and severity of central nervous system depression (decreased) or withdrawal (enhanced clearance) shortly after birth [2, 3].

Secondly, as advocated by international organizations such as the World Health Organization, the majority of neonates are breastfed. The mean contribution of postnatal exposure of the newborn to tramadol through mother's milk (3%) has been recently described based on observations collected in 75 breastfeeding mothers treated with tramadol for post-caesarian analgesia [4]. In the specific setting of 2–3 days postnatal exposure of neonates whose mothers were not treated with tramadol before delivery, the exposed infants had similar characteristics, including Apgar scores at birth and neurologic and adaptive capacity scores compared to controls. Once again, these observations are mean values and were collected in the specific setting of post-caesarean analgesia. Therefore, they may not represent the complete spectrum of interindividual variability. Following a single case of fatal poisoning in a breastfed newborn after maternal codeine intake, the link between

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maternal CYP2D6 polymorphisms and both maternal and neonatal sedation has recently been documented in a case-control study for codeine [5, 6]. Two maternal covariates of the interindividual variability in neonatal central nervous system depression were documented: the dose administered and CYP2D6 polymorphism.

Based on the above summarized observations on aspects of pharmacokinetics and pharmacodynamics of moderately potent opioids, we would like to argue that the advice formulated (i.e. “long-term treatment with tramadol during pregnancy should be limited to carefully selected cases”) is only a partial answer to the clinical management for both mother and child. Adequate perinatal management should take into account both the mother and the fetus/newborn. Management of maternal pain and avoidance of maternal withdrawal during pregnancy are crucial aspects of perinatal care for both mother and fetus. In early postnatal life and based on the extensive interindividual variability in tramadol disposition in neonates, clinical management of the newborn should consider signs of both sedation and withdrawal.

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