Tramadol withdrawal in a neonate after long-term analgesic treatment of the mother

C. Willaschek, E. Wolter, R. Buchhorn

Eur J Clin Pharmacol (2009) 65:429–430
DOI 10.1007/s00228-008-0598-z

LETTER TO THE EDITORS

Tramadol withdrawal in a neonate after long-term analgesic treatment of the mother

C. Willaschek · E. Wolter · R. Buchhorn

Received: 20 November 2008 / Accepted: 24 November 2008 / Published online: 16 December 2008

Keywords Tramadol · Newborn · Withdrawal syndrome

Dear Sir,

Tramadol is frequently used in treatment of intermediate to severe pain. As it has a low affinity for opioid receptors it is considered a substance with lower risk for development of drug abuse, dependance or withdrawal syndrome. Among adults tramadol withdrawal after long-term treatment is reported occasionally [1, 5].

Case report We treated the infant of a mother who suffered from chronic low back pain. As long-term analgesic treatment she received tramadol 400 mg/day. During the last weeks of pregnancy, the tramadol dose was reduced to 200 mg/day. Because of gestational diabetes and fetal macrosomia, caesarian section was performed at 36 weeks of gestational age. Birth weight was 4060 g (279 g >P97), length was 52 cm (P85), and head circumference was 37 cm (0.4 cm >P97). Apgar score was 9-10–10 at 1, 5 and 10 min. There were no signs of diabetic fetopathy.

On the second day of life, at 35 h of age the infant showed signs of severe withdrawal syndrome with high-pitched crying, trembling, and shortened sleeping hours. Substitution therapy with tinktura opii achieved acceptable symptom control. Over 13 days we were able to reduce and finally stop substitution.

Profound sleep myoclonia, which was clearly diagnosed by normal electro-encephalography, was reported to persist. Neurological follow-ups showed normal results.

Measurement from chord blood found 630 ng tramadol ml^{-1} (therapeutic range 100-800 ng/ml, toxic range >1000 ng/ml). Measurement from venous blood on the first day was 805 ng tramadol ml^{-1}. At 6 days of age, a second measurement showed <50 ng tramadol ml^{-1}.

Discussion As a synthetic 4-phenyl-piperidin analogon of codein, tramadol binds with low affinity with μ-opioid receptors. Furthermore it obtains non-opioid properties through inhibition of norepinephrine and serotonin reuptake.

Main metabolisation is performed by N- and O-desmethylation and conjugation with glucuronacid and sulphate. O-demethyl-tramadol-hydrochlorid (M1) acts as the main analgesic. N-desmethyl-tramadol (M2) is described as an additional active metabolite. Metabolisation is catalysed by the cytochrome P450 isoenzyme CYP2D6 mainly through the M1 pathway, as well as several others such as CYP3A4 and CYP2B6 mainly in M2. Half-life is reported for adults as 430 min for tramadol and 330 min for M1. A study on the pharmacokinetics of tramadol in infants after treating the mother for labour pain measured a half-life of 420 min for tramadol. It led to a remarkably prolonged estimated half-life of 5097 min (sic) for M1 in neonates [2]. Delayed excretion of M1 seems to be due to the reduced glomerular filtration rate of the infant (about 30% of adult GFR) and to the higher amount of

C. Willaschek (✉) · R. Buchhorn
Klinik für Kinder- und Jugendmedizin, Caritaskrankenhaus,
Uhlandstr. 7,
97980 Bad Mergentheim, Germany
e-mail: christian.willaschek@ckbm.de

E. Wolter
Klinik für Anästhesiologie und Intensivmedizin,
Caritaskrankenhaus,
Uhlandstr. 7,
97980 Bad Mergentheim, Germany

extracellular fluid causing a relatively larger distribution volume. Immaturity in the glucuronidation and sulfation pathways, which are involved in the conjugation of M1, may play an additional role in prolonged elimination [3].

Despite reductions in maternal analgesic therapy, the infant showed clear symptoms of opioid withdrawal at 35 h of age. Compared to neonatal withdrawal syndromes after maternal substitution with methadone or buprenorphin, we observed a rather early impact of symptoms as well as a shorter clinical course. The latter seems to be connected with the half-life of M1 rather than with the half-life of tramadol itself and shows similarity with the case reported by Meyer et al. [4]. Measurement of M1 unfortunately was not available at that time.

Although only a small amount of tramadol is expected to be excreted in the breast milk and breast feeding should be possible without increased risk [7], the mother chose to bottle-feed formula milk. Feeding problems were not reported at the time.

Considering the widespread use of tramadol [6], this rare and anecdotal report of neonatal withdrawal syndrome raises some concerns. Restricting long-term treatment of pregnant women with opioid analgesics to strict indications may be a possible solution. Considering this severe withdrawal, although symptoms have been held under control, long-term treatment with tramadol during pregnancy should be limited to carefully selected cases.

References

1. Barsotti CE, Mycyk MB, Reyes J (2003) Withdrawal syndrome from tramadol hydrochloride. Am J Emerg Med 21(1):87–88
2. Claahsen-Van Der Grinten HL, Verbruggen I, Van Den Berg PP, Sporken JM, Kollee LA (2005) Different pharmacokinetics of tramadol in mothers treated for labour pain and in their neonates. Eur J Clin Pharmacol 61(7):523–529
3. Johnson TN (2005) Different pharmacokinetics of tramadol in mothers treated for labour pain and in their neonates. Towards an increased knowledge of paediatric clinical pharmacology. Eur J Clin Pharmacol 61(12):929–930
4. Meyer FP, Rimasch H, Blaha B, Banditt P (1997) Tramadol withdrawal in a neonate. Eur J Clin Pharmacol 53(2):159–160
5. Ripamonti C, Fagnoni E, De Conno F (2004) Withdrawal syndrome after delayed tramadol intake. Am J Psychiatry 161 (12):2326–2327
6. Schaefer C, Spielmann H, Vetter K (2006) Arzneiverordnung in Schwangerschaft und Stillzeit, 7th ed. Urban & Fischer Verlag, München, p 49
7. Schaefer C, Spielmann H, Vetter K (2006) Arzneiverordnung in Schwangerschaft und Stillzeit, 7th ed. Urban & Fischer Verlag, München, p 582