



International Journal of Case Reports (ISSN:2572-8776)



Inadvertent epidural administration of remifentanil (Ultiva®) during labour analgesia

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ABSTRACT

The use of remifentanil patient-controlled analgesia for labour analgesia remains controversial. The high potency of the drug, the fear of serious adverse drug reactions and drug administration errors are all legitimate concerns. We report the case of a woman in labour who inadvertently received a remifentanil solution via epidural route. In addition to the risk of respiratory depression, the epidural administration of remifentanil contains glycine in its solution and is therefore contraindicated due to potential neurological injury. The patient received a total of 2 mg of remifentanil and 15 mg of glycine in her epidural over a long period before the error was identified. Interestingly the patient was mostly comfortable during labour and fortunately no maternal or neonatal adverse events occurred.

Keywords: remifentanil; glycine; epidural; obstetrical analgesia; medical errors; human factor

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How to cite this article:

Dany Khodr. Inadvertent epidural administration of remifentanil (Ultiva®) during labour analgesia . International Journal of Case Reports, 2019 4:75

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Introduction

Epidural analgesia is considered the gold standard for labour analgesia¹. Intravenous remifentanyl (Ultiva®, GlaxoSmithKline Manufacturing SpA, Verona, Italy) patient-controlled analgesia (PCA) can be used as an alternative to epidural analgesia^{2, 3, 4}. However, its use in obstetrics remains controversial and is currently an “off-label” use. Many anaesthetists fear the potential serious maternal and neonatal drug-related complications⁵. Among those some may be due to drug administration issues or errors, including wrong dosage, wrong drug, wrong patient or wrong route. Here we describe the case of a parturient who accidentally received an epidural infusion of a remifentanyl PCA during a 7 hours period.

Case report

A nulliparous woman was admitted at term to the maternity for immediate induction of labour following spontaneous rupture of membranes. Her vital signs at admission were normal. Following patient consent, a combined spinal-epidural anaesthesia was performed at L3-L4 level at 11:45 am. Induction of neuraxial analgesia consisted of an intrathecal injection of bupivacaine and opioid. Analgesia maintenance was intended to be done using a programmed intermittent epidural bolus (PIEB) using a mixture of bupivacaine 0.0625% with fentanyl 2 mcg/ml (programmed bolus 8ml, interval 40min, rescue bolus 5ml with a 15 min lockout interval). However, a PCA pump containing remifentanyl 20 mcg/ml in a 100 ml bag (prepared for another patient) was inadvertently connected to the

epidural catheter instead of the PIEB pump with 250 ml of the epidural solution. After the spinal injection a bilateral T10 sensory level was achieved and the patient was comfortable. She was informed on the use of the PCEA and how request additional rescue bolus. The error remained unnoticed. Four hours and fifty minutes later, the anaesthetist was called during the first stage of labour. The patient was complaining of pain in her lumbar and sacral areas. There was a bilateral T10 sensory block but no sensory block in the sacral territories. The anaesthetist administered a supplementary epidural bolus of 8 ml of bupivacaine 0.125% with 75 mcg of clonidine.

The medication error was only discovered seven hours after its occurrence. At that time, the entire 100 ml remifentanyl solution had been administered (10 boluses of 8 ml and 4 boluses of 5 ml). During this interval the patient was continuously monitored. Her blood pressure was automatically recorded every 15 min (range, 104/70 to 131/87 mmHg), cardiac rate remained around 61-84 bpm, and oxygen saturation between 97.5-98.5%. No signs of respiratory depression nor decrease level of consciousness were observed. Continuous cardiotocography was within normal with a foetal heart rate between 120-160 bpm, except for five brief episodes of bradycardia (90-100 bpm), variability was normal.

An immediate neurological examination reported no motor blockade and a describe T9 sensory level on both sides. Oxygen saturation was above 97%. The patient was comfortable and

the cervix dilatation was complete. A standard PIEB solution was placed and a 5ml rescue bolus was immediately injected, followed 20 minutes later, by a supplementary epidural bolus of 8 ml of bupivacaine 0.125%. The midwife, obstetrician and neonatologist teams were immediately informed about the drug error and the need for continuous monitoring of the patient vital signs, neurological status and foetal monitoring. The patient was informed one hour after stopping the remifentanil infusion and an hour later she delivered a healthy baby (Apgar score, 9/10/10). The patient vital signs remained normal during a two-hour surveillance and she was then transferred to the regular post-delivery unit.

During several postpartum visits, patient examination was normal with no residual sensory-motor block, itching, headache or pain. When asked retrospectively, she did not report any impression of sedation, dizziness, thoracic or rigidity oppression, or dyspnoea during or after labour.

Discussion

Epidural administration of remifentanil is contraindicated. In addition to risk of respiratory depression, it contains glycine as an acidic buffer which carries the potential risk of neurological injury⁶. In animal studies, the intrathecal administration of glycine caused hind limb twitching, pain, convulsions in dogs⁶ and motor impairment in rats⁷. This case reports the inadvertent epidural administration of 2mg remifentanil containing 15 mg of glycine over a 7-hour period without any neurological,

haemodynamic or respiratory consequences and with a relative efficacy on labour pain.

Three cases of inadvertent remifentanil epidural administration infusion were previously reported in the literature⁸⁻¹⁰. All due to a drug administration errors during perioperative care of patients undergoing surgery under general anesthesia combined with epidural analgesia. None of them occurred in the obstetrical setting. Major adverse effects with severe respiratory depression requiring orotracheal intubation, chest rigidity and unconsciousness^{8,9}, as well as dizziness, but no persistent neurological consequences were reported. These patients received high dose of epidural remifentanil through rapid injected bolus or in continuous infusion. Conversely, our patient received several intermittent boluses of various dosages (160 or 100 mcg) over a 7-hour period. The PCA pump that we used has an infusion rate of 100 ml/min (Micrel Rythmic Evolution® pump, Micrel Medical Devices SA, Athens, Greece). The epidural boluses were therefore administered relatively slowly at a rate of 100 ml/min corresponding to 33.3 mcg of remifentanil per minute. The remifentanil pharmacokinetics in the epidural space have never been studied. However, according to pharmacokinetic models¹¹⁻¹³, only 3 min are necessary to achieve a 50% decrease in remifentanil blood drug concentrations after termination of an intravenous infusion and 11 min to achieve 80%. This very short half-life, combined with an unknown proportion of the drug been systemically reabsorbed from the epidural space, probably explain why our patient did not

present obvious signs or symptoms of remifentanil overdose.

After identifying the drug error, we feared potential neurological complications⁶ or motor impairment⁷ as reported in animal studies after intrathecal administration of glycine. This patient received a total of 15 mg of epidural glycine. Fortunately, the neurological examination excluded convulsions or twitching and confirmed normal sensory and motor functions. Although there is a clear difference between intrathecal and epidural injection, the theoretical risk of nerve tissues damage can not be excluded after inadvertent epidural injection of glycine, moreover if a combined spinal epidural anaesthesia is performed. Even though such case has never been described we would only recommend careful and serial neurological examinations after a similar incident as we did with the patient.

Epidural opioids are believed to be absorbed by the cerebrospinal fluid and act on receptors of the dorsal horn of the spinal cord, inhibiting the release of substance P. This mechanism has the advantage of producing analgesia without blocking motor or sympathetic nerve fiber¹⁴. Remifentanil may have had that effect in our patient and explain why the patient was at least partially relieved during a 7-hour periods. Interestingly, the patient started to feel serious discomfort 20 min after we stopped the remifentanil infusion, however, at that time she was at full dilatation of the cervix. Interestingly, a similar delay in the systemic effect was observed in another case report where the patient required

intubation 13 min after receiving a 300 mcg remifentanil epidural bolus. This delay may be explained by the diffusion of remifentanil from the epidural space to systemic blood or cerebrospinal fluid^{9,11,12}.

This drug administration error resulted from multiple causes. First and foremost, the same PCA pump model was used for all the different programmes (i.e., intravenous PCA, PIEB and PCEA) regardless of the contained solution and the route of administration. This clearly opened the door to potential human error^{15,16} that could have had serious consequences. In addition, several failures in the safety process contributed to occurrence of the error and its late recognition. The remifentanil PCA pump was initially prepared for another patient but unused and left in the room where the PIEB pumps were stored. Finally, the bedside control of the drug administered was not performed before connecting the infusion to the epidural catheter.

After this incident new measures were taken in order to avoid its reoccurrence in the labour ward. Different labels for each pump with dedicated programs were implemented. A dedicated place was created if a remifentanil pump needed to be stored. Use of the Neurax® NR-fit system (Neurax, Shipley, UK), which combines a safety enhancement by making the connectors dimensionally and mechanically incompatible with the standard ISO Luer, are currently considered. If a Neurax®-fitted device is used, drugs cannot be injected into blood vessels and those intended to enter into the

bloodstream via a normal 'Luer' syringe cannot be injected into the spinal or epidural space¹⁷.

In conclusion, this is the first report where remifentanyl was inadvertently injected into the epidural space of a parturient who did not suffer any side-effects and who also received a relative analgesic efficacy.

There were no fundings or conflict of interests.

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