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REVIEW ARTICLE

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Remifentanil for labor analgesia: an evidence-based narrative review

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ABSTRACT
This manuscript reviews the available literature on remifentanil patient-controlled intravenous analgesia in labor focusing on efficacy and safety. Remifentanil compares favorably to other potent systemic opioids but with fewer opioid-related neonatal effects. However, remifentanil provides modest and short-lasting labor analgesia that is consistently inferior when compared to neuraxial analgesia. The initial analgesic effect provided with remifentanil also diminishes as labor progresses. In several studies, remifentanil induced significant respiratory depressant effects in laboring women with episodes of desaturation, hypoventilation and even apnea. Given the safety concerns, we recommend that remifentanil patient-controlled intravenous analgesia should not be a routine analgesia technique during labor. In cases where neuraxial analgesia is refused or contraindicated and the use of remifentanil justified, continuous and careful monitoring is required to detect respiratory depression to provide safe care of both the pregnant woman and unborn child.

Introduction

Neuraxial labor analgesia is well established worldwide, especially in developed countries. However, many women, even in the developed world, do not opt for neuraxial analgesia, have no access to this form of pain relief, or have contraindications to its use. Many laboring women therefore receive parenteral opioid-based analgesia using pethidine (meperidine), fentanyl, butorphanol, nalbuphine, tramadol, morphine, alfentanil or sufentanil. Remifentanil is a potent opioid with pharmacological properties that potentially makes it an ideal parenteral analgesic for labor. For the last two decades, remifentanil has been studied as either an alternative to neuraxial analgesia or as the preferred parenteral opioid to treat labor pain. Despite the increased use of remifentanil patient-controlled intravenous analgesia (PCIA) to provide labor analgesia, this indication is considered off-label use. Remifentanil carries a Category C label (unknown whether the drug can cause fetal harm when administered to a pregnant woman) for use in pregnancy. Additionally, the manufacturers state "the safety of remifentanil during labor or delivery has not been demonstrated" and "the drug should be given to a pregnant woman only if clearly needed benefit justifies the potential risk to the fetus." (Ultiva® (remifentanil) package insert 2013, Mylan Institutional LLC, Rockford, IL, USA).

For this review, we conducted a literature search with no language restriction on 31 December 2014. Searches were performed in PubMed using the terms "remifentanil" and "labor analgesia" or "PCIA remifentanil and labor analgesia". The results of the search are reported in Table 1. Articles were selected based on relevance to this narrative review on the efficacy and safety of remifentanil for the provision of labor analgesia. The class of recommendation and level of evidence is stated for each recommendation.

Remifentanil pharmacokinetics

Remifentanil has a very short context-sensitive half-time in non-pregnant humans of three minutes,[1] regardless of the duration of infusion. It is rapidly broken down to non-active metabolites by non-specific plasma esterases independent of organ metabolism. Kan et al. demonstrated that remifentanil rapidly and

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Table 1 Medline search of articles on remifentanil for labor analgesia

Publication breakdown	Number of papers
Total	135
Not related to topic	33
Basic research	4
Case reports	13
Reviews and meta-analysis	18
Editorials and letters	22
Surveys/audits	6
Trial protocol publication	1
Original clinical studies:	38
Initial feasibility studies	9
Comparison with other opioids	8
Comparison with nitrous oxide	2
Comparison with epidural analgesia	10
Administration modalities	7

extensively crosses the placenta with a uterine vein to maternal artery concentration of 0.88.[2] In addition, the uterine artery to uterine vein concentration ratio of 0.29 suggests rapid fetal metabolism and/or redistribution. The authors also noted low plasma concentrations in pregnant women following infusion compared to a similar infusion in non-pregnant individuals. This might be explained by increases in remifentanil clearance, an altered volume of distribution, low plasma protein clearance and an increase in non-specific esterase activity. Jost et al. highlighted large patient variability in pregnant individuals and underlined the need for a pregnancy-specific pharmacokinetic model.[3] Ngan Kee et al. confirmed the high trans-placental passage following a bolus at induction of anesthesia for cesarean delivery.[4]

Theoretically, the rapid onset and offset of remifentanil with effect-site concentration peaking at 1–2 min might be beneficial for labor analgesia, especially if timing of remifentanil peak effect can be matched to uterine contractions. However, given the duration of a contraction to be 60–80 seconds, the peak remifentanil effect might only be achieved during the next contraction. Authors have proposed that remifentanil delivery could be optimized if based on contraction pattern predictions.[5] Clinically, however, many subjects do not have regular or predictable contractions making timing of remifentanil peak effect to the contraction peak difficult. The clinically observed large patient variability, underlined in studies like that by Jost, might be partially explained by heterogeneity in uterine contractions as labor progresses.[3] The impact of 'patient-training' to optimize the timing of remifentanil administration to coincide with contractions has not been evaluated. Vital-sign integrated drug delivery systems as proposed by Sia et al. may have the potential to improve the safety of remifentanil PCIA.[6]

Current practice

A wide variety of remifentanil PCIA administration protocols and settings have been investigated (Table 2). A bolus of 20–40 μg (0.25–0.5 μg/kg) is used most widely with a lockout of 1–5 min. Background infusions are less frequently applied due to maternal side effects and safety concerns, but are occasionally used as they may improve analgesic efficacy.[7]

In Europe, remifentanil PCIA is increasingly used either as a primary mode of labor analgesia or as an alternative to neuraxial analgesia, when the latter is contraindicated. However, this practice is not uniform over Europe. Saravanakumar et al. surveyed UK practice in 2006 and reported that 50% of units used PCIA opioid analgesia in labor and 35% of these units used remifentanil PCIA.[8] Tveit et al. surveyed practice in Norway in 2005 and 2008 and noted that remifentanil PCIA was used infrequently, in only 2–8% of units, whilst pethidine was used in 77% of units.[9] One in four women used neuraxial analgesia in this survey. Schnabel et al. surveyed practice in Germany in 2010 and noted that remifentanil PCIA was only used in 4% of units.[10] A French practice survey by Hanouz et al. in 2011 found that remifentanil PCIA was used in 52% of units as alternative to neuraxial analgesia when the latter was contraindicated.[11] In a Belgian survey of labor analgesia practice, Lavand'homme and Roelants reported that remifentanil was the first choice opioid alternative when neuraxial analgesia was contraindicated.[12] Since 2009, the use of remifentanil has grown significantly in Switzerland. Under the patronage of the Swiss Association of Obstetric Anaesthesia, The RemiPCA SAFE Network was established to continuously monitor the use of remifentanil PCIA in labor nationwide. To date, 24 obstetric units continuously report on all patients in whom remifentanil PCIA was used either as first-line labor analgesic option or as alternative when neuraxial analgesia was contraindicated.[13]

Analgesic efficacy

Thirty-six original studies, which evaluated the use of remifentanil PCIA for labor analgesia, were identified from our literature search (Table 1). The breakdown consisted of: feasibility studies (n=9); comparisons with other opioids (n=8); comparisons with nitrous oxide (n=2); comparisons with epidural analgesia (n=10); and studies investigating the modalities of administration (n=7). Three meta-analysis and systematic reviews were also identified that summarized selected results. The class of recommendation and level of evidence as developed by the ACCF/AHA Task Force on Practice Guidelines are provided.[14]