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SAFETY OF REMIFENTANIL IN PREGNANCY

Question:
What is the safety of remifentanil in pregnancy?

Answer:
Remifentanil has been allocated an FDA pregnancy category C meaning that *"studies have shown that the drug exerts animal teratogenic or embryocidal effects, but there are no controlled studies in women, or no studies are available in either animals or women"* [1].

First trimester
We are not aware of any reports that describe the use of remifentanil in the first or second trimester of pregnancy[1-4].
In general, short-term use of opioids such as morphine are considered relatively safe in pregnancy. Limited information has associated first trimester exposure to codeine (metabolised to morphine) with an increased incidence of foetal malformations. However, the data is conflicting and the influence of confounders such as maternal disease state and other drug therapy cannot be excluded. It is prudent to avoid all drug exposure in the first trimester where possible.

Third trimester
Remifentanil has a rapid onset and a relatively short duration of action as denoted by the brief 'context-sensitive' half-time of 3-5 minutes (the 'context-sensitive' half-time is described as being the time for the plasma concentration to decrease by 50% after stopping the infusion). The terminal elimination half-life is around 10 minutes in adults[5,6]. These properties suggest that remifentanil may offer advantages in obstetrics by minimising opioid exposure to the foetus/neonate.

Studies/case series: Intravenous remifentanil has been trialed for patient-controlled analgesia (PCA) during labour[7-11]. In one study (n=21), bolus doses of 0.25-1.0mcg/kg with a 2-min lockout were used, with or without a background infusion of 0.025-0.05mcg/kg/min. A significant reduction in foetal heart rate was not observed, and Apgar scores and cord blood gases remained within normal limits[7].
Six women received remifentanil 25mcg with a 5-min lockout above a continuous infusion of 0.05mcg/kg/min. Satisfactory analgesia was reported and all mothers remained alert or drowsy but readily rousable. Side effects such as nausea and pruritus were not observed in the mothers. None of the infants had side effects[8].
Five women received a remifentanil PCA because of contraindications to epidural analgesia (e.g. thrombocytopenia)[9,10]. There was no evidence of adverse foetal outcomes aside from one episode of maternal sedation and foetal heart rate decelerations in one mother-infant pair[9].
A small double-blind trial randomised nine women to receive boluses of remifentanil 0.5mcg/kg with a 2-min lockout (no maximum dose per hour), while eight women received pethidine 10mg with a 5-min lockout (maximum 100mg/h). Remifentanil was more effective at reducing pain as measured using a visual analogue scale and the study was stopped early because of significantly lower Apgar scores in the pethidine group[11].

Seventeen women received an intravenous infusion of remifentanil 0.1mcg/kg/min as part of non-urgent Caesarean sections. They also received an epidural of lignocaine with adrenaline. The protocol allowed the anaesthetist to increase the remifentanil infusion dose, administer additional intravenous boluses of remifentanil or additional epidural lignocaine. The mean cord blood:maternal blood ratio was 0.88 +/- 0.78. Neonatal Apgar scores, Neurologic and Adaptive Capacity scores were all within normal limits[12].

In contrast to the studies outlined above, all four subjects in one study withdrew because of inadequate analgesia and opioid related side effects (e.g. nausea, brief desaturation episodes, pruritus). The dose was 0.25mcg/kg with an increase of 0.125mcg/kg increments if analgesia was inadequate (maximum of 0.5mcg/kg)[13]. Other authors argued that remifentanil was an ideal obstetric analgesic and suggested that one of the reasons for inadequate analgesia in this study was administration by a third party (an anaesthetist) rather than by PCA[14,15]. Patient education may have allowed early dosing on anticipation of pain of contraction. Dhileepan and Stacey[14] also commented that they used higher doses starting at 0.5mcg/kg (the maximum dose allowed in Olufolabi's study) and increased the dose by 50% if analgesia was inadequate.

Case reports: Two women with compromised cardiac function received remifentanil as part of anaesthesia for Caesarean section[16,17]. One infant received 20mcg of naloxone intramuscularly (apparently as a precaution against opioid related side effects) but was otherwise healthy[16]. The second infant was described as being in *"excellent condition"* and did not require tracheal intubation, mask ventilation or naloxone[17].

An infusion of remifentanil 0.2-1.0mcg/kg/min was used as a component for anaesthesia for Caesarean section at 36 weeks' gestation. The infant was born seven minutes after initiation of the remifentanil infusion and had normal umbilical cord pH and spontaneous ventilation and respiratory efforts. Apgar scores were 7 and 8 at one and five minutes due to decreased muscle tone. The infant received supplemental oxygen because of pallor, but had an uneventful recovery[18].

Remifentanil was used in a dose of 2mcg/kg followed by 0.075-0.15mcg/kg/min during emergency Caeserean section for a patient with mitral valve disease, asthma and pre-eclampsia. There was no evidence of clinically significant respiratory depression in the neonate at delivery. Apgar scores were 6 and 8 at one and five minutes[19].

Two women undergoing emergency caesarean section received remifentanil without complications affecting status of either mother or child[20].
Remifentanil was used as part of general anaesthesia for Caesarean section in a woman at 27 weeks' gestation with severe pre-eclampsia with thrombocytopenia[21]. She delivered a small 635g baby with Apgar scores of 3, 5 and 10 at one, five and ten minutes, respectively. Intubation was required initially but the baby started spontaneous breathing soon after. The baby remained ventilated for 24 hours.

Conclusions:

We are not aware of any information describing the use of remifentanil in the first trimester of pregnancy. The limited information on the use of this agent in the latter trimesters suggests stringent use may be associated with minimal effect on the newborn. As always, risk:benefit assessment is required with any drug use in pregnancy. In this case, the short half-life of remifentanil suggests that it may be a useful opioid for use in obstetrics.

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