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RESEARCH PAPER

Transplacental transfer of remifentanil in the pregnant ewe

JB Coonen[1], MAE Marcus[1], EAJ Joosten[1], M van Kleef[1], C Neef[2], H van Aken[3] and W Gogarten[3]

[1]*Department of Anaesthesiology, MUMC, Maastricht, The Netherlands,* [2]*Department of Clinical Pharmacy & Toxicology, MUMC, Maastricht, The Netherlands, and* [3]*Department of Anaesthesiology, University Hospital of Münster, Münster, Germany*

Background and purpose: While remifentanil can be used either during labour or fetal surgery, more should be known about the transplacental transfer of this opioid. The aim of this study was to investigate the placental transfer and haemodynamic effects of remifentanil after i.v. administration to pregnant ewes.
Experimental approach: Seven pregnant ewes received a continuous infusion of remifentanil (0.33 $\mu g \cdot kg^{-1} \cdot min^{-1}$) for 1 h, and maternal and fetal arterial blood samples were drawn at regular intervals during and up to 1 h after the discontinuation of the infusion. Haemodynamic parameters were monitored continuously. Blood gas samples were drawn at baseline and once during the infusion.
Key results: Peak maternal remifentanil plasma levels of 4.0 ± 0.9 $ng \cdot mL^{-1}$ (mean ± SD) and peak fetal plasma levels of 0.4 ± 0.3 $ng \cdot mL^{-1}$ were obtained. Remifentanil plasma levels dropped rapidly after the discontinuation of the infusion. The continuous infusion of remifentanil did not result in significant maternal or fetal haemodynamic changes.
Conclusions and implications: Remifentanil rapidly passes through the placenta of pregnant ewes and although remifentanil concentrations stay significantly lower in the fetus compared with those in the mother, remifentanil can be detected in significant amounts in the fetus.
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Keywords: labour pain; maternal–fetal exchange; remifentanil; obstetrical anaesthesia

Abbreviations: P_{aCO2}, partial pressure of carbon dioxide; P_{aO2}, partial pressure of oxygen; Sa_{O2}, oxygen saturation; $t_{1/2}$, elimination half-life

Introduction

During analgesia for labour or anaesthesia for caesarean section, there is a major concern that the administration of opioids, via the i.v., intramuscular or epidural route, can result in significant placental transfer, compromising the neonate at birth. On the other hand, in the evolving field of fetal surgery, the choice of opioids should be based on a high placental transfer to ensure adequate fetal analgesia during surgery, while being readily metabolized by the fetus after surgery.

In the latter situation, remifentanil, an ultra-short acting 4-anilidopiperidine opioid with μ-selective opioid activity could prove particularly useful, as it has high lipid solubility with an octanol/H_2O partition coefficient of 17.9, predicting a high placental transfer. Remifentanil possesses an ester side chain that is rapidly hydrolysed by non-specific plasma and tissue esterases (Egan, 1995). Its metabolism is independent of renal or hepatic function, making it suitable for use in patients with hepatic or renal failure (Dershwitz *et al.*, 1996; Hoke *et al.*, 1997). In adults it has been shown that the clearance of remifentanil is independent of dose, body weight, age and gender (Westmoreland *et al.*, 1993). In fetuses with immature hepatic metabolism these unique features might also be advantageous. Because of the esterase-based metabolism that results in an extremely short context-sensitive half-life time of 3 min (Kapila *et al.*, 1995), prolonged fetal respiratory depression is unlikely to occur.

The aim of our study was to investigate the placental transfer and haemodynamic effects of remifentanil in the pregnant ewe.

Methods

Surgery

All animal care and experimental protocols were approved by our institutional committee and the district government of

Correspondence: Joris B Coonen, Department of Anaesthesiology, MUMC, Universiteitssingel 50, Postbus 616 (Box 38), 6229 ER Maastricht, The Netherlands. E-mail: j.coonen@np.unimaas.nl
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Münster, Germany. Pregnant ewes (n = 7) with a mean gestational age of 120 days (range 118–122 days, term 145 days) were chronically instrumented, as described previously (Vertommen *et al*., 1995). Briefly, animals were anaesthetized with halothane in oxygen, orotracheally intubated and mechanically ventilated. Anaesthesia was maintained with halothane (1–1.5 Vol%) in air, and a catheter was inserted into the superior vena cava, via the left jugular vein using a sterile cutdown technique. Using the same incision, a polyvinyl catheter was inserted into the carotid artery and tightly secured. A median laparotomy was performed and a 20 MHz Doppler flow probe (Baylor College of Medicine, Houston, TX, USA) secured around a main branch of the uterine artery, supplying the pregnant horn. The uterus was carefully incised and a hind limb of the fetus exteriorized. A polyvinyl catheter was advanced into the fetal aorta via the tibial artery. After insertion of a catheter into the amnion cavity, lost amniotic fluid was replaced with warmed sterile saline and the uterotomy carefully closed. Fetal catheters and the leads of the Doppler flow probe were tunnelled subcutaneously and exteriorized through a small incision in the maternal flank. After closure of the laparotomy, anaesthesia was discontinued. To ensure that the anaesthesia given during this preparation of the animals did not interfere with the experiment, we waited 3 days before starting the experiments. During the recovery period, animals had free access to food and water and were examined daily for overall wellbeing. Particular attention was paid to food and fluid intake, body temperature and possible premature contractions. Furthermore, the surgical wounds were inspected and all catheters were flushed with heparinized saline. Ewes received an antibiotic regimen consisting of kefzol 2 g i.v., gentamicin 80 mg i.v. and gentamicin 80 mg intra-amniotic on the day of surgery and the first day after surgery.

Placental transfer

After the recovery period of 3 days and a stabilization period of 30 min, baseline parameters were recorded and remifentanil (Glaxo Smith Kline, Genval, Belgium) was given to the mother through the jugular vein at a rate of 0.33 $\mu g \cdot kg^{-1} \cdot min^{-1}$, without prior bolus for 60 min, after which the infusion was stopped. Maternal carotid artery and fetal aortic blood samples were drawn at baseline and at 5, 15, 30, 61, 65, 75 and 120 min during and after the infusion respectively. Maternal and fetal arterial blood samples were drawn simultaneously by two different investigators.

Maternal and fetal blood samples were immediately mixed with citric acid (20 $\mu g \cdot mL^{-1}$ blood) to halt the *ex vivo* hydrolysis of remifentanil and stored at −70°C until further analysis. Remifentanil plasma level determinations were performed by Glaxo Smith Kline, Genval, Belgium, using gas chromatography high resolution mass spectrometry with selected ion monitoring (Grosse *et al*., 1994). The relative standard deviation over the whole concentration range was <5% with a correlation better than 98%. Remifentanil plasma concentrations below the limit of detection (0.05 $ng \cdot mL^{-1}$) were excluded from the analysis.

Haemodynamic analysis

During the experiments, maternal heart rate, maternal mean arterial pressure, fetal heart rate, fetal mean arterial pressure, amniotic pressure and uterine blood flow were measured continuously, using a standard cardiovascular monitor (Marquette Hellige GmbH, Freiburg, Germany) and a continuous wave Doppler system (Baylor College of Medicine, Houston, TX, USA) connected to a Macintosh computer (Power Macintosh 8500/120, Apple Computer Inc., Cupertino, CA, USA) with Lab View Software (Version 4.0.1. National Instruments, Austin, TX, USA) installed. Fetal heart rate was derived from the fetal arterial pressure curve and fetal mean arterial pressure was corrected for amniotic pressure. Maternal cardiac output was calculated as the mean of three consecutive cardiac output measured with the thermodilution technique. At baseline and 45 min after the start of administration of remifentanil, blood gas analyses were performed in fetal and maternal blood samples (ABL Radiometer, Copenhagen, Denmark).

Results

Remifentanil plasma levels

Remifentanil arterial plasma levels were measured over time in both the mother and fetus. In Figure 1, the raw data from all the animals are shown. From the start of the infusion, maternal remifentanil plasma levels showed a steep increase reaching average peak maternal plasma levels of 4.0 ± 0.9 $ng \cdot mL^{-1}$ (mean ± SD) (n = 7). After the discontinuation of the infusion, maternal remifentanil plasma levels declined rapidly. Fetal remifentanil plasma levels increased less steep compared with maternal remifentanil plasma levels reaching average peak fetal plasma levels of 0.4 ± 0.3 $ng \cdot mL^{-1}$ (mean ± SD) (n = 7).

Our data demonstrated an increase of the fetal/maternal plasma concentration ratio from 0.1 to 0.3, from 30 min after the start of the infusion to 5 min after the discontinuation of the infusion.

Pharmacodynamic analysis

In the experiments performed, the continuous infusion of remifentanil 0.33 $\mu g \cdot kg^{-1} \cdot min^{-1}$ did not result in significant maternal or fetal haemodynamic changes. Maternal and fetal blood gases did not change significantly during remifentanil administration (Table 1). Pregnant ewes did not exhibit any respiratory depression with continuous administration of remifentanil at this dose (0.33 $\mu g \cdot kg^{-1} \cdot min^{-1}$).

Discussion

This study shows that remifentanil rapidly crossed the placenta in pregnant ewes and could be detected in the fetus after an infusion of a clinically relevant dose.

Pharmacokinetic data on the use of remifentanil in obstetric patients are scarce. So far, only two studies have been published, evaluating a low dose of remifentanil (0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$) during caesarean section under epidural anaesthesia (Kan *et al*., 1998) or a bolus of 1.0 $\mu g \cdot kg^{-1}$ at the

start of induction (Kee *et al*., 2006). Kan *et al*. (1998) reported an umbilical vein/maternal artery ratio of remifentanil plasma levels of 0.88. In our study the fetal/maternal concentration ratio was 0.1 at steady state. The umbilical vein/maternal artery ratio in the study of Kan *et al*. (Kan *et al*., 1998) can be explained by an already declining maternal and fetal drug concentration after discontinuation of remifentanil with plasma levels not being at a steady state. Another explanation for the difference seen in fetal/maternal concentration ratios between our and Kan *et al*.'s study could result from their reported difficulty in obtaining maternal arterial blood samples in six out of 16 patients, thereby increasing their umbilical vein/maternal artery ratio. These data were nevertheless included in their experiments. Interestingly in another study (Kee *et al*., 2006) an almost similar umbilical vein/maternal artery ratio of 0.73 was obtained, similar to that reported in the earlier study of Kan *et al*. (1998). A single bolus of 1.0 $\mu g \cdot kg^{-1}$ remifentanil was given. Although a single bolus at induction might be well suited to attenuate the response to tracheal intubation, the maternal and fetal remifentanil plasma levels might already be declining at the moment the remifentanil plasma levels were determined as was the case in the study of Kan *et al*. (Kan *et al*., 1998). Although the placental transfer of remifentanil during caesarean section has already been reported in humans (Kan *et al*., 1998; Kee *et al*., 2006), in general, measurements of human fetal blood concentrations are only possible at a single time point, making evaluation of fetal/maternal concentration ratios more prone to misinterpretation. The latter easily happens if maternal and fetal drug concentrations have not yet reached a steady state or start to decline (Anderson *et al*., 1980). These authors (Anderson *et al*., 1980) have stated that care should be taken in calculating placental transfer and fetal drug exposure, if plasma levels are only taken at a single time point, not knowing, if mother and fetus are truly in a steady state. Calculations derived from single-time point measurements have resulted in misleading interpretations of active placental secretion of drugs into the fetus (Anderson *et al*., 1980). In our study the fetal/maternal plasma concentration ratio increased from 0.1 to 0.3 from 30 min after the start of the infusion to 5 min after the discontinuation of the infusion. This change in fetal/maternal plasma concentration ratio from 0.1 to 0.3 over time supports the idea that proper transplacental transfer evaluation is only possible if blood samples are taken at different time points. Studies in chronically instrumented pregnant sheep enable serial blood sampling to evaluate the time course of placental transfer, fetal distribution and elimination more closely. Continuous sampling would be the perfect sampling method. Particularly with remifentanil that has a very short $t_{1/2}$ (elimination half-life), if a sample is taken just before or after the discontinuation of the infusion, significantly different plasma concentrations will be obtained.

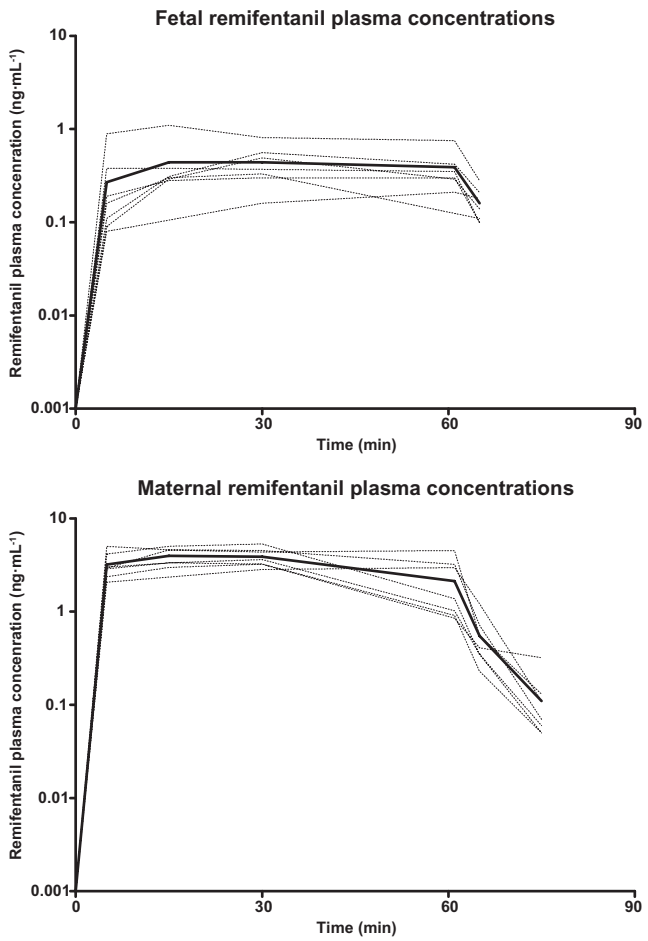

Figure 1 Upper: changes in fetal remifentanil plasma concentrations ($ng \cdot mL^{-1}$; note log scale) after 0.33 $\mu g \cdot kg^{-1} \cdot min^{-1}$ i.v. remifentanil administration during 60 min over time; $n = 7$; individual animals are represented by dotted thin line; mean is represented as the superimposed thick line. Lower: changes in maternal remifentanil plasma concentrations ($ng \cdot mL^{-1}$; note log scale) after 0.33 $\mu g \cdot kg^{-1} \cdot min^{-1}$ i.v. remifentanil administration during 60 min over time; $n = 7$; individual animals are represented by dotted thin line; mean is represented as the superimposed thick line.

Table 1 Blood gas analysis

Time (min)	*Baseline*		*15*	
	Ewe	*Fetus*	*Ewe*	*Fetus*
pH	7.55 ± 0.02	7.37 ± 0.02	7.56 ± 0.03	7.35 ± 0.03
P_{aO2}	96.9 ± 3.7	15.4 ± 0.9	102.9 ± 3.7	16.3 ± 1.5
P_{aCO2}	28.5 ± 1.5	44.3 ± 2.1	28.9 ± 1.5	46.6 ± 2.4
Sa_{O2}	99.0 ± 0.5	46.8 ± 4.0	99.2 ± 0.6	44.5 ± 6.9

Values are mean ± SEM ($n = 7$).
P_{aCO2}, partial pressure of carbon dioxide; P_{aO2}, partial pressure of oxygen; $Sa_{O2.}$, oxygen saturation.

Chronically instrumented pregnant sheep are the most common species used to evaluate placental drug transfer and have been extensively used to examine the placental transfer of opioids like fentanyl (Craft *et al*., 1983) and sufentanil (Vertommen *et al*., 1995). But experiments from sheep may not reflect placental drug transfer in humans, for example because of the different nature of the placenta. While the sheep placenta is epitheliochorial, the human placenta is haemochorial. The lower permeability of epitheliochorial placentas influences especially the transfer of hydrophilic compounds with low molecular weights, whereas the effect on transfer of lipophilic compounds is less pronounced. The highly lipid-soluble opioid methadone readily diffuses across the placenta and can be detected in fetal plasma in significant amounts (Szeto *et al*., 1982). To our knowledge, no animal studies have been performed so far for analysis of maternal to fetal drug transfer of the lipid-soluble remifentanil. Possible differences in levels and activity of plasma and tissue esterases, hydrolysis at the level of the placenta and protein binding might also contribute to the differences in values we found in our sheep model from those from studies in humans (Kan *et al*., 1998; Kee *et al*., 2006). Unfortunately, to our knowledge, data on the extent of metabolism of remifentanil at the level of the placenta and protein binding in sheep is not known. The elimination of remifentanil seemed to be slower in the fetus than in the mother, explaining the increase in fetal/maternal plasma concentration ratios. This is in contrast with the findings of Ross *et al*. (2001) who found that the elimination of remifentanil, in contrast with other opioids, is very rapid in neonates. On the other hand, Chan (1995) reported a lower blood cholinesterase level in the newborn, compared with adults. Our study deals with fetuses in which a lower blood cholinesterase level could result in the slower decline in plasma levels of remifentanil. As the elimination of remifentanil is independent of renal or hepatic function and plasma-esterase activity appears to be the main elimination mechanism, we suggest that plasma-esterase activity in the mother could be different from that in the fetus.

The absence of respiratory depression in our study is in agreement with published reports that suggest that sheep are very resistant to the pharmacodynamic effects of opioids. Grant *et al*. studied the anti-nociceptive effect of different analgesics in sheep and found that buprenorphine, methadone and flunixin meglumine did not produce an analgesic response in doses used in humans (Grant *et al*., 1996). The α_2-adrenoreceptor agonist, xylazine, on the other hand produced an analgesic response. These findings make extrapolation of our pharmacodynamic results to the human situation complex.

Due to the low potency of remifentanil's metabolite GR90291 and its failure to lead to increased side effects in patients with end-stage liver disease or end-stage renal disease, we did not determine its plasma levels in the fetus. It has been concluded that its overall pharmacological effect is negligible (Dershwitz *et al*., 1996). An accumulation of the metabolite in renal insufficiency did not increase the amount of side effects, even though concentrations were increased 25-fold (Hoke *et al*., 1997).

A dose of 0.33 $\mu g \cdot kg^{-1} \cdot min^{-1}$ remifentanil is sufficient for surgical anaesthesia in humans, making the concomitant administration of isoflurane during an opioid/nitrous oxide-based anaesthesia unnecessary in the majority of patients and is well above the ED_{50} for skin incision (Dershwitz *et al*., 1995). Neonatal pharmacokinetics and pharmacodynamics although might be quite different from adults and so far, it is not known which plasma levels of remifentanil will still be pharmacologically effective in the newborn or fetus. In a study from Van de Velde *et al*. (2005) fetal immobilization was reached with a remifentanil infusion rate of 0.115 ± 0.020 $\mu g \cdot kg^{-1} \cdot min^{-1}$. In an earlier study from these authors (Van de Velde *et al*., 2004) general anaesthesia for caesarean section with remifentanil 0.50 $\mu g \cdot kg^{-1}$ followed by 0.20 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and propofol resulted in brief neonatal respiratory depression in 60% of uncompromised neonates. For sufentanil, protein binding is lower and elimination half-life is significantly longer in neonates compared with adults (Greeley *et al*., 1987; Meistelman *et al*., 1990). Therefore care should be taken when advocating remifentanil for delivery or caesarean section, even though the pharmacokinetics of remifentanil possesses major advantages over other opioids in this setting.

In our study, we found that the fetal/maternal ratio is only 0.1. This implies that if using remifentanil for fetal surgery, it should be given directly to the fetus ensuring that the fetal plasma level did not depend on placental transfer.

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Conflicts of interest

None.

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