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Intravenous Remifentanil

Placental Transfer, Maternal and Neonatal Effects

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Background: **Remifentanil has not been studied in obstetric patients. This study evaluates the placental transfer of remifentanil and the neonatal effects when administered as an intravenous infusion.**

Methods: **Nineteen parturients underwent nonemergent cesarean section with epidural anesthesia and received 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ remifentanil intravenously, which was continued until skin closure. Maternal arterial (MA), umbilical arterial (UA), and umbilical venous (UV) blood samples were obtained at delivery for analysis of drug concentrations of remifentanil, its metabolite, and blood gases. Maternal vital signs were monitored continuously, and pain and sedation levels were assessed intermittently. Apgar scores were obtained at 1, 5, 10, and 20 min, and Neonatal and Adaptive Capacity Scores were noted 30 and 60 min after delivery. Parturients and newborns were observed for at least 24 h after surgery for side effects.**

Results: **The means and SDs of UV:MA and UA:UV ratios for remifentanil were 0.88 ± 0.78 and 0.29 ± 0.07, respectively. Mean clearance was 93 $ml \cdot min^{-1} \cdot kg^{-1}$. The mean UV:MA and UA:MV ratios for remifentanil acid were 0.56 ± 0.29 and 1.23 ± 0.89, respectively. The mean MA (remifentanil acid):MA (remifentanil) ratio was 2.92 ± 3.65. There were no adverse effects on the neonates, but there was a sedative effect and respiratory depressant effect on the mothers.**

Conclusions: **Remifentanil crosses the placenta but appears to be rapidly metabolized, redistributed, or both. Maternal sedation and respiratory changes occur, but without adverse neonatal or maternal effects. (Key words: Analgesia; obstetrics; opioids.)**

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REMIFENTANIL, the hydrochloride salt of 3-[4-methoxycarbonyl-4-[(1-oxopropyl)phenylamino]-1-piperidine] propanoic acid, methyl ester, is a new ultrashort-acting anilidopiperidine with μ-specific opioid activity. Studies with remifentanil demonstrate cardiovascular and side-effect profiles similar to those of other fentanyl congeners.[1,2] Unique to the phenylpiperidines, however, is an ester linkage that makes remifentanil susceptible to rapid hydrolysis by nonspecific blood and tissue esterases.[1] This type of metabolism accounts for its very short context-sensitive half-time (3 min)[3] in nonpregnant patients regardless of the duration of the infusion (the context-sensitive half-time is an estimation of the time required for a 50% decrease in central compartment drug concentration after the discontinuation of an infusion that maintained a constant serum concentration).[1,3] In addition, remifentanil's metabolism is independent of renal and hepatic function, making it unique among opioids.[4-6] The primary metabolite, remifentanil acid (formerly known as GR90291), has only a small fraction ($^1/_{300}$-$^1/_{4,600}$) of the activity of remifentanil in animal studies and is excreted primarily by the kidneys.[7,8]

Recent studies have investigated the pharmacology of

remifentanil in varied clinical settings.[9-16] However, the present study is the first to focus on obstetric patients, for whom the unique properties of remifentanil may impart particular benefit. The goals of this prospective, randomized, double-blinded study were to determine the extent of placental transfer of remifentanil and the neonatal and maternal effects when remifentanil is administered as an intravenous adjunct to regional anesthesia for cesarean section delivery.

Materials and Methods

The committees on human research at the University of California San Francisco and the Kaiser Permanente Medical Center of San Francisco approved the study. Each patient gave written informed consent. Parturients older than 18 yr who were between 37 and 40 weeks gestation and eligible for a routine epidural anesthetic for a nonemergent cesarean section delivery were included in the study. Parturients considered at high risk (for example, those with preeclampsia, uncontrolled hypertension, valvular heart disease, poorly controlled diabetes mellitus, renal disease, severe asthma, or severe anemia) were excluded from the study. Parturients with a multiple gestation, substance abuse history, hypersensitivity to opioids, or a psychiatric illness were also excluded.

Nineteen parturients were studied. All patients received 30 ml of a nonparticulate antacid orally and a 1-2 l intravenous crystalloid bolus before anesthetic administration. A lumbar epidural catheter was placed in each patient using a standard loss-of-resistance technique followed by a test dose of 2% lidocaine (3 ml) with epinephrine (1:200,000). All parturients then received an epidural solution of 2% lidocaine with epinephrine (1:200,000) in divided doses to establish a level of anesthesia appropriate for cesarean section (sensory level ~ T4). An intravenous infusion of remifentanil (Glaxo-Wellcome, Research Triangle Park, NC) was administered to the patients at a dose of 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ after dosing of the epidural catheter with lidocaine. Skin incision was postponed until at least 15 min after initiation of the intravenous infusion. The intravenous infusions were continued until skin closure.

The anesthesiologist caring for the patient was allowed to use clinical judgment to increase the intravenous remifentanil infusion, administer additional 2% epidural lidocaine or administer an intravenous bolus of

Table 1. Response Criteria*

Hypotension
SBP <100 mmHg before delivery
SBP <90 mmHg after delivery
Hypertension
SBP >160 mmHg
DBP >100 mmHg
Bradycardia
<50 bpm
Pain score of 2 (moderate); (0 = none; 1 = mild; 2 = moderate; = severe)
Sedation score of ≥3 (1 = fully awake; 2 = drowsy; 3 = eyes closed but arousable by command; 4 = eyes closed but arousable by physical stimulation; 5 = eyes closed and not arousable)
Respiratory depression: RR <12 breaths/min
Oxygen saturation: <95%

SBP = systolic blood pressure; DBP = diastolic blood pressure; RR = respiratory rate.

* Adjustments were made in the study IV remifentanil infusions, either increased or decreased as appropriate based on the response criteria shown in the table.

remifentanil (16.7 μg/ml). The protocol also allowed two reductions in the intravenous infusion dose before mandatory discontinuation of the infusion (Table 1 lists the criteria for intervention). Each decrease in the infusion was to one half the existing rate. An increase in the infusion was equivalent to increasing the dose by 0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$. All patients received 3-5 mg epidural morphine and oxygen at a rate of 3-5 l/min by mask. The dose of epidural morphine was that used by the anesthesiologists in their routine clinical practice and was administered after the fetus was delivered.

Maternal arterial (MA) and umbilical venous (UV) and umbilical arterial (UA) cord blood samples were obtained for analysis of blood gases and concentrations of remifentanil and remifentanil acid after delivery. Umbilical cord blood samples were taken from a double-clamped segment of umbilical cord and placed in tubes containing citric acid (10 μg/ml serum) and mixed immediately. Maternal blood samples were obtained from the radial artery and processed as just described with citric acid. Samples were stored at −20°C. Gas chromatography with high-resolution mass spectrometry-selected ion monitoring was used to determine the remifentanil and metabolite concentrations.[17,18] Blood gas analysis was obtained using the technology available at the medical center where the cesarean section was performed. Clearance was calculated using the following equation: CL = infusion rate/C_{MA} (steady state mater-

nal artery remifentanil concentration immediately before delivery).

Blood samples excluded from drug analysis included those from patients who received an intravenous bolus of remifentanil immediately before delivery, those from patients in whom the infusion was stopped before delivery, and umbilical cord samples retrieved >3 min after the segment was clamped. In these patients, the serum level of remifentanil was not at a steady state, making drug analysis invalid.

Neonates were evaluated by Apgar scores at 1, 5, 10, and 20 min and Neurologic and Adaptive Capacity Scores[19] were noted at 30 and 60 min. Neonates were observed for side effects occurring within 24 h of delivery.

Maternal blood pressure, heart rate, oxygen saturation, respiratory rate, and pain and sedation scores were recorded at predetermined times: 15 min before and 15 min after initiation of the intravenous infusion, and again at skin incision, bladder retraction, fetal delivery, uterine exteriorization and repair, skin closure, and then 5 and 10 min after discontinuing the intravenous infusion (pain and sedation scores were based on four- and five-point scales, respectively). Intervention was required based on criteria listed in table 1. Blood pressure, heart rate, and oxigen saturation were obtained using standard operating room monitors. Respiratory rates were monitored by clinical observation (counting). Maternal side effects and treatment were monitored during the cesarean section and for 24 h after delivery. Treatment of side effects was at the discretion of the anesthesiologist.

Results

Intravenous infusion rates were decreased before delivery in 3 of 17 parturients because of transient hypotension (n = 1) and subjective excessive sedation (n = 2), although the criteria for excessive sedation, respiratory depression, and arterial oxygen desaturation were not met before rate reductions. After delivery, five parturients required a decrease in their infusions. Dizziness was the reason for one of the cases, whereas excessive sedation was responsible for the other four alterations. During the study, eight patients required a decrease in their infusion and one received an intravenous rescue bolus.

Data from 16 patients were analyzed to determine remifentanil serum concentrations. Included in analyses were blood samples from one of the pilot studies in which the protocol was followed successfully. Data from four parturients were excluded from analysis for the following reasons: inadequate serum sample (n = 1), termination of the intravenous infusion before delivery (n = 1), and failed epidural anesthetics (n = 2); one failed epidural was converted to a general anesthetic and the other to a spinal anesthetic, and the patients were withdrawn from the study.

Table 2. Blood Remifentanil Concentrations

	Remifentanil		Remifentanil Acid	
	n	Mean ± SD	n	Mean ± SD
MA (μg/ml)*	16	1.32 ± 0.80	13	2.42 ± 1.55
UV (μg/ml)	15	0.73 ± 0.27	12	1.33 ± 0.78
UA (μg/ml)	10	0.20 ± 0.07	8	1.47 ± 0.84
UV/MA	15	0.88 ± 0.78	10	0.56 ± 0.29
UA/UV	10	0.29 ± 0.07	7	1.18 ± 0.82
Drug administration and clearance† (n = 16)				
Mean total dose (μg)				286 ± 122
Mean total dose/kg (μg/kg)				3.56 ± 1.36
Mean clearance ($ml \cdot min^{-1} \cdot kg^{-1}$)				93.1 ± 71.9

* Mean MA remifentanil concentration for patients whose infusions were at 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 15 min at time of blood sampling was 1.52 + 0.74 ng/ml (n = 13).

† Values are expressed as mean ± SD.

The mean UV:MA ratio was 0.88 ± 0.78 and the UA:UV ratio was 0.29 ± 0.07 (table 2). The mean total remifentanil dose administered during the surgery was 286 ± 122 μg, and the clearance was 93 ± 71.92 $ml \cdot min^{-1} \cdot kg^{-1}$. Table 2 lists the MA, UV, and UA remifentanil blood concentrations and the UV:MA and UA:UV ratios. The total number of samples varies due to inadequate blood volume or inability to obtain blood. Ratio data (UV:MA, UA:UV) were derived only from data in which both samples were obtained from the same patient. Table 2 lists results of the analysis of the primary metabolite, remifentanil acid. In the MA, UV, and UA samples, the mean concentrations of the metabolite were 2.41 ± 1.61 ng, 1.34 ± 0.82 ng, and 1.53 ± 0.89 ng, respectively. The mean UV:MA ratio was 0.56 ± 0.29 and the UA:UV ratio for the metabolite was 1.23 ± 0.89. The mean MA (remifentanil acid):MA (remifentanil) ratio was 2.92 ± 3.65.

Respiratory rates ranged from 16–23 breaths/min. Oxygen saturation during the study period ranged from 91–100%. Blood pressure, heart rate, and pain

Table 3. Maternal Arterial Blood Gas Data

Parameter	Value
*p*H	
n	16
Mean	7.36 ± .03
Range	7.32–7.42
Pa_{CO_2} (mmHg)	
n	16
Mean	36.8 ± 3.1
Range	29–42
Pa_{O_2} (mmHg)	
n	16
Mean	171 ± 38.8
Range	91–24
Sa_{O_2} (%)*	
n	14
Mean	98.9 ± 0.7
Range	97–99.5

Values are mean ± SD.

* Sa_{O_2} not routinely available at one institution involved in the study.

Table 4. Newborn Apgar Scores and Neurobehavioral and Adaptive Capacity Scores (NACS)

Time	Value
Newborn Apgar Scores (n = 17)	
1 min	
Median	8
Range	4–9
% >7	84
5 min	
Median	9
Range	8–9
% >7	100
10 min	
Median	9
Range	9–10
% >7	100
20 min	
Median	9
Range	9–10
% >7	100
Neurobehavioral and Adaptive Capacity Scores (NACS) (n = 17)	
30 min	
Median	37
Range	35–39
% >35	100
60 min	
Median	35
Range	34–39
% >35	82

scores were not remarkable. Sedation scores were higher at skin incision, bladder retraction, delivery, during uterine repair, and 5 min after the discontinuation of the intravenous infusion (fig. 1). Maternal blood gas analysis (table 3) revealed increased partial carbon dioxide tensions (Pa_{CO_2}) and lower *p*H values. Maternal arterial blood samples could not be obtained from one parturient because of technical difficulties. At one facility, the oxygen saturation value was not routinely part of the blood gas analysis.

Results of Apgar scores recorded at 1, 5, 10, and 20 min were within normal limits. All neonates had Apgar scores >7 at 5 min (table 4). Neurologic and Adaptive Capacity Scores noted at 30 and 60 min were within normal limits (table 4). Umbilical cord blood

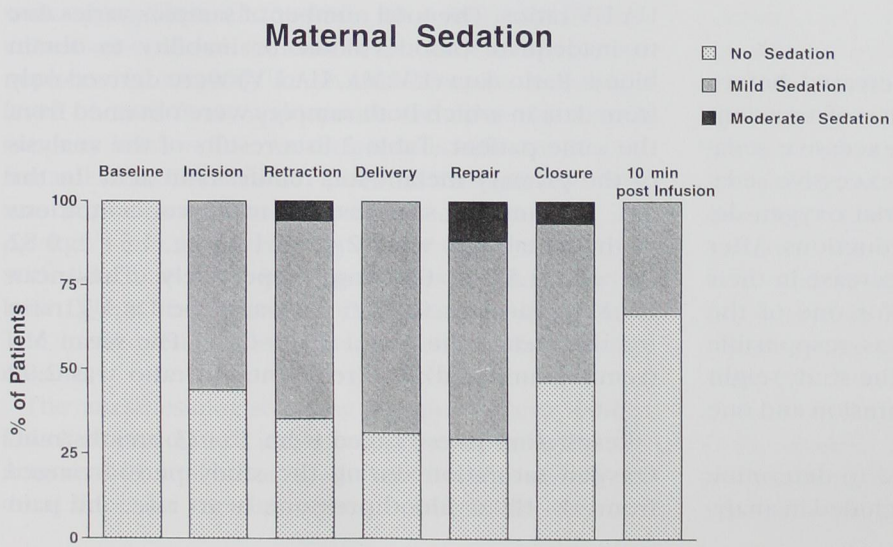

Fig. 1. Maternal sedation assessments are shown at specific time points in the operating course. Patients receiving remifentanil developed mild-to-moderate sedation (2 to 3 sedation score, table 1) until the infusion was discontinued. No patient scored a 4 or 5 (severe sedation) on the sedation scale (table 1). R = remifentanil, n = 17.

Table 5. Umbilical Cord Blood Gases

	Umbilical Vein	Umbilical Artery
*p*H		
n	16	16
Mean	7.27 ± .06	7.22 ± .06
Range	7.07–7.34	7.02–7.28
P_{CO_2} (mmHg)		
n	16	16
Mean	51.1 ± 7.6	60.6 ± 11.2
Range	42.0–70.6	41.0–84.0
P_{O_2} (mmHg)		
n	16	16
Mean	29.8 ± 5.1	15.1 ± 4.8
Range	20.0–36.0	5.3–26.5
Sa_{O_2} (%)*		
n	15	14
Mean	46.9 ± 12.6	14.9 ± 7.2
Range	25.5–64.7	2.2–27.3

Values are mean ± SD.

* Sa_{O_2} not routinely available at one of the institutions involved in the study.

gas analysis showed increased mean UV carbon dioxide pressure (P_{CO_2} values; table 5).

Discussion

The primary goal of this study was to determine the placental transfer of remifentanil. We also sought to determine its effects on the mother and neonate when given as an intravenous adjunct to epidural anesthesia for cesarean section. We found that remifentanil rapidly crosses the placenta and no deleterious effects on neonates nor parturients were apparent with the dose studied; however, the maternal sedation observed with the dose studied is in contrast to previously published work in nonpregnant patients.

The mean remifentanil UV:MA ratio of 0.88 ± 0.78 in this study suggests a significant degree of placental transfer. Considering the high lipid solubility of remifentanil (octanol-water partition coefficient of 17.9 at a *p*H of 7.4) and generous placental perfusion, this ratio seems more reasonable than the lower value (approximately 0.20) suggested in animal studies,** and is similar to the UV:MA ratio of sufentanil (0.81), as reported by Loftus *et al.*[20] after epidural administration for labor.

** Glaxo Wellcome Inc., Research Triangle Park, North Carolina. Unpublished internal documents.

The mean remifentanil UA:UV ratio of 0.29 ± 0.07 suggests rapid metabolism and rapid redistribution of the drug in the fetus. However, it is uncertain what magnitude to attribute to either factor. No data exist establishing the half-life of remifentanil nor its degree of redistribution in a human or animal fetus. In a study of adult male volunteers receiving an intravenous infusion of remifentanil[21] (1–8 $\mu g \cdot kg^{-1} \cdot min^{-1}$ over 20 min), the mean volume of distribution at steady state was 31.8 ± 7.4 l, suggesting extensive extravascular distribution and some component of redistribution that might account for the low UA:UV value found in our study. Nevertheless, both Westmoreland *et al.*[22] and Egan *et al.*[21] found rapid clearance of remifentanil (2.8–5.0 l/min). In addition, animal and human studies have shown that, despite variable high bolus doses and prolonged intravenous infusion of remifentanil, the pharmacokinetics and duration of the clinical effect remain comparable (unlike the phyenylpiperidines).[23,24] This is consistent with the very short context-sensitive half-time reported by Kapila *et al.*[3] and suggests minimal extravascular accumulation of remifentanil, which has obvious potential benefits to the mother and fetus.

In evaluating the pharmacology data, we assumed that a steady state was achieved in both the parturient and the fetus when the blood samples were drawn. The intravenous infusion dose in the study was derived from previous studies in nonobstetric patients receiving regional anesthesia and remifentanil as an intravenous adjunct sedative-analgesic and with consultation with Glaxo-Wellcome.[16,25] Preclinical animal studies (Glaxo-Wellcome Inc.)** suggested limited transfer of remifentanil (the fetal remifentanil concentration was one fifth of the maternal concentration). In addition, it was thought that placental esterases might be significant in decreasing placental transfer of remifentanil. However, in the preclinical animal studies, samples were taken 30 min after a single intravenous bolus of remifentanil, and conceivably placental transfer would have been higher if administered as an intravenous infusion and allowed to establish a steady state before samples were drawn.

The higher mean UA remifentanil metabolite (remifentanil acid) level of 1.53 ± 0.89 ng/ml compared with the mean UV remifentanil metabolite level of 1.34 ± 0.82 ng/ml suggests continued metabolism of remifentanil. Possibly, the low remifentanil UA:UV ratio (0.29 ± 0.07) is ultimately due to drug metabolism by blood or tissue esterases after redistribution. Nevertheless, it could be argued that the level of these enzymes is re-

duced in the fetus and extrapolation of the degree of metabolism in the fetus from data in adults is inaccurate. Furthermore, the obvious limitation of our study, in this regard, is that the sampling of blood only at delivery represents only one point in time, which may not accurately reflect the newborn drug level. Additional studies are needed to clarify this question.

Interestingly, the mean clearance found in the remifentanil group was 93.1 $ml \cdot min^{-1} \cdot kg^{-1}$, which is greater than twice the value derived by Glass *et al.*[23] in nonobstetric patients (41.2 $ml \cdot min^{-1} \cdot kg^{-1}$). The physiologic changes associated with pregnancy (larger blood volume, increased cardiac output, and renal perfusion) may account for this difference. Gerdin *et al.*[26] also reported a greater clearance of morphine in the parturient. The mean maternal serum concentration of 1.52 ng/ml in our study with an infusion rate of 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ is less than one half the value reported by Dershwitz *et al.*[2] (3.2 ng/ml) in men and nonpregnant women. Although an increase in clearance in a parturient may account for this difference, other possible factors include an altered volume of distribution, a lower plasma protein concentration, or both, and an increase in nonspecific esterase activity.

The mean MA (remifentanil acid):MA (remifentanil) ratio was 2.92 ± 3.65, which is consistent with the longer terminal half-life of the metabolite described by Westmoreland *et al.*[22] Although the metabolite tends to linger, this does not appear to be clinically important because animal studies suggest that the potency of the metabolite is only $^1/_{300}$ to $^1/_{4,600}$ that of remifentanil.[7,8]

Neonatal Outcome

All neonates were vigorous (Apgar score >7) at the time of the 5-min Apgar score. Umbilical cord blood-gas analysis identified slightly increased UV P_{CO_2} values, which was consistent with the slightly elevated MA P_{CO_2} values in the parturients, consistent with a clinically evident opioid effect. Nevertheless, all umbilical cord blood gas values were within the acceptable range[27] (*p*H 7.32–7.42; Pa_{CO_2} 29–42 mmHg), and the neonates exposed to remifentanil were not adversely affected.

Maternal Outcome

Sedation scores increased at incision, bladder retraction, delivery, during uterine repair, and 5 min after the intravenous infusion was discontinued (fig. 1). Unfortunately, the exact duration of excessive sedation (score >2) was not monitored precisely. If a parturient achieved a sedation level >2, the time of onset was recorded but the moment when the sedation level returned to 2 was not consistently recorded.

Preliminary data suggest that the ED_{90} for a level 2 sedation score is 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in nonobstetric patients.[25] This dose provided a greater level of sedation in the 17 parturients who received remifentanil (5 of 17 parturients achieved sedation levels of 3). Whether physiologic changes that occur during pregnancy (for example, elevated serum progesterone levels) increase the sensitivity to remifentanil is unclear. Previous studies comparing nonpregnant women and men found no correlation between sex alone and the sensitivity to remifentanil.[7] Interestingly, recent data from a study by Drover and Lemmens[28] suggest that nonpregnant women may require a higher remifentanil serum concentration than men.

Methods

An area of concern was the collection of blood samples. In 6 of the 16 patients, maternal arterial samples were obtained 4 min after delivery or were not obtained because of technical difficulties. An arterial catheter placed before operation would have been ideal, but this approach was not practical. In addition, there were problems obtaining sufficient umbilical cord blood samples for pharmacologic analysis. This loss of data motivated us to include the pharmacologic data from one of the pilot studies. Future studies may quantify placental transfer more accurately.

Future Role of Remifentanil in Obstetric Anesthesia

The potential role of remifentanil in obstetric anesthesia is intriguing. Its rapid onset and offset could be used to assist in blunting the hemodynamic changes associated with laryngoscopy in a patient with preeclampsia or a patient with significant cardiac disease in which a predominantly opioid general anesthetic is preferred. The rapid offset of remifentanil would eliminate the potential prolonged respiratory depressant and sedative effects on the parturient or neonate, which may occur with the other opioids currently available. In addition, because its metabolism is independent of liver and renal function, patients with dysfunction in either of these organs could benefit from the sedative and analgesic properties of remifentanil without the problems of drug accumulation and exaggerated effects associated with the other opioids.

Remifentanil also may prove beneficial in a patient-

controlled delivery system such as patient-controlled analgesia or patient-controlled epidural analgesia. In laboring patients not eligible for or not desiring regional analgesia but still in need of some analgesia, remifentanil administered *via* patient-controlled analgesia might prove an intriguing option. The rapid onset and offset would allow easy titration of the opioid and also would provide the "control" some parturients desire in their labor management. Intravenous remifentanil has now been used in a parturient in great pain to provide transient analgesia and sedation to allow placement of an epidural.[29] Although the spinal pharmacology of remifentanil is being investigated,[30,31] there is no preparation of remifentanil currently available that can be administered intraspinally. The current preparation has resulted in reversible motor impairment after continuous intrathecal administration in rats.[30] Both the glycine and the *p*H of the preparation are suspected because the intrathecal injection of the acidic glycine vehicle alone has resulted in reversible motor weakness and apparent dysesthesia.[31] However, the cause is still being investigated. At the present time, remifentanil is not recommended for epidural or intrathecal use. Potential exists, however, if an intraspinal preparation is ultimately available, to use remifentanil in combination with a local anesthetic for epidural or spinal anesthesia–analgesia for cesarean section or labor (possibly in a patient-controlled epidural analgesia delivery system) and take advantage of its pharmacokinetic properties.

Conclusions

When administered as an intravenous infusion, placental transfer of remifentanil occurs rapidly. In the fetus, the drug is metabolized and apparently redistributes quickly, although this study evaluated blood samples only at one time (*i.e.*, delivery). Both the Apgar scores and Neurologic and Adaptive Capacity Scores demonstrated alert newborns with minimal clinically important effects of opioid administration, despite the presence of clinical maternal sedation. Although the rapid metabolism of remifentanil suggests that it may be uniquely beneficial in the practice of obstetric anesthesia, additional studies are needed to evaluate its potential.

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