Remifentanil Degradation in Umbilical Cord Blood of Preterm Infants

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ABSTRACT

Background: No pharmacokinetic data about remifentanil in preterm infants exist, although remifentanil is increasingly used in this especially vulnerable subgroup of pediatric patients. Unfortunately, ethical restrictions in the volume of blood that can be withdrawn for kinetic sampling nearly prohibit pharmacokinetic studies in preterm infants.

Methods: Because remifentanil is rapidly metabolized by nonspecific blood esterases, we collected umbilical cord serum of preterm and term infants to investigate whether the activity of nonspecific blood esterases depends on gestational age. Umbilical cord serum, buffer solution, ascorbic acid, and remifentanil were mixed in a glass vial placed in a shaking water bath at 37°C. Subsequently, serum samples were subjected to liquid chromatography–mass spectrometry-based analysis of remifentanil and its metabolite GR90291 after 0, 30, 60, 100, and 150 min.

Results: We analyzed umbilical cord serum samples of 34 preterm infants (24–36 gestational weeks) and six term infants. The degradation rates of remifentanil to its major metabolite GR90291 were comparable in preterm and term infants. The overall median degradation half-life of remifentanil was 143 ± (interquartile range) 47 min (minimum, 76 min; maximum, 221min) without significant differences between very preterm infants (less than 28 gestational weeks) and term infants. The remifentanil concentration remained stable in control runs without serum.

Conclusions: Our study demonstrates that very preterm infants exhibit a high nonspecific esterase activity in umbilical cord blood that is comparable with that of term infants. These results support clinical experiences that remifentanil is rapidly metabolized by preterm infants without prolonged side effects.

What We Already Know about This Topic

- Remifentanil appears to have a short-lasting effect in preterm neonates, but for ethical reasons its pharmacokinetics have not been studied

What This Article Tells Us That Is New

- With the use of umbilical blood to assess nonspecific esterase metabolism of remifentanil, blood from preterm neonates was found to be similar to term neonates in the rate of remifentanil metabolism

IN term neonates as well as in preterm infants, intense pain should be treated with potent opioids. The most frequently used opioids in pediatric anesthesia and neonatal intensive care medicine are morphine and fentanyl.[1,2] However, neonatologists fear the exceptionally prolonged side effects of these substances in preterm infants. Side effects such as constipation or respiratory depression with the need for prolonged mechanical ventilation may have a major effect on morbidity in this especially vulnerable subgroup of pediatric patients.[3]

Remifentanil is structurally unique among currently available opioids because of its ester linkage, which makes it susceptible to hydrolysis by nonspecific esterases in blood and tissues. The major metabolite of remifentanil, GR90291, is almost inactive compared with remifentanil and is eliminated primarily by the kidneys.[4–6] Because of its unique pharmacokinetic property (a short recovery profile), remifentanil could be the ideal opioid for preterm infants.[7,8] Four studies investigating the pharmacokinetics of remifentanil in children have been published.[9–12] They demonstrate that pharmacokinetic data in children are comparable with those in adults. However, until now no pharmacokinetic data have existed about remifentanil in preterm infants.[13]

Ethical restrictions in the volume of blood that can be withdrawn for kinetic sampling nearly prohibit pharmacoki-

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Address correspondence to Dr. Welzing: University of Cologne, Children's Hospital, Department of Neonatology and Pediatric Intensive Care, Kerpener Strasse 62, 50937 Cologne, Germany. lars.welzing@uk-koeln.de. Information on purchasing reprints may be found at www.anesthesiology.org or on the masthead page at the beginning of this issue. ANESTHESIOLOGY's articles are made freely accessible to all readers, for personal use only, 6 months from the cover date of the issue.

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netic studies in preterm infants. However, in contrast to other opioids, the metabolism of remifentanil is almost independent of liver and renal function.[14,15] Because remifentanil is rapidly metabolized by nonspecific blood esterases, umbilical cord blood is suitable for *in vitro* investigations.[8,16] Using this exceptionally huge amount of fetal blood, we wanted to investigate whether the activity of nonspecific blood esterases depends on gestational age. Our aim was to find out whether very premature infants exhibit a blood esterase activity comparable with that of mature infants.

Materials and Methods

Patients

The study was approved by the Ethical Review Board of the Medical Faculty of the University of Cologne (Cologne, Germany). Informed consent was given by the parents or legal guardians of the children.

Because we wanted to investigate whether the activity of nonspecific blood esterases depends on gestational age, we collected umbilical cord blood of all available preterm infants with 24–36 weeks of gestation, who were born between August 2007 and August 2008 in the Department of Obstetrics and Gynaecology, University Hospital of Cologne, Germany. For the statistical analysis, we subdivided the preterm infants into three groups: 24–27 gestational weeks (group P1), 28–31 gestational weeks (group P2), and 32–36 gestational weeks (group P3). In addition, we collected umbilical cord blood from six term infants (group T).

Blood Sampling. One minute after umbilical cord clamping, we carefully aspirated 1–5 ml fetal blood from the placental part of the umbilical vein. Blood samples were transferred into an S-monovette, total volume 10 ml (Sarstedt AD & Co., Nümbrecht, Germany) and centrifuged immediately at room temperature and 3,000 *g* for 10 min (Minifuge GL; Hereaeus-Christ, Osterode, Germany). Subsequently, the supernatant was transferred as a serum sample into microvials and directly frozen at −80°C for later *in vitro* investigation.

In Vitro Enzyme Kinetics

Chemicals and Reagents. The following chemicals were used for the analytical procedure. Acetonitrile was purchased from Roth (Karlsruhe, Germany). Formic acid, sodium chloride, potassium chloride, disodium hydrogen phosphate, potassium dihydrogen phosphate, and ascorbic acid were purchased from Merck (Darmstadt, Germany). All reagents were of analytical or high-performance liquid chromatography (HPLC) grade. Deionized water, further purified with a Milli-Q water-purifying system (Millipore Corporation, Bedford, MA) was used. HPLC eluent A was water with 0.1% formic acid. Acetonitrile was used as HPLC eluent B. Remifentanil hydrochloride, methyl 1-(3-methoxy-3-oxopropyl)-4-(phenyl-propanoylamino) piperidine-4-carboxylate; remifentanil metabolite GR90291, and internal standard (propionamide ester oxalate, GR92559A) were purchased from GlaxoSmithKline (Durham, United Kingdom).

Experimental. A sample volume of 0.5 ml umbilical cord blood serum was mixed with 0.5 ml phosphate-buffered saline (phosphate buffer, pH 7.4; 300 mM) and 10 μl ascorbic acid (12.5%, percentage by mass) in a 10-ml glass vial placed in a shaking water bath at $\upsilon = 37$°C (shaking water bath 20; Medingen, Dresden, Germany) for 5 min. An aliquot of 52.5 μl precooled ($\upsilon = 5$°C) remifentanil stock solution containing 1 mg/l remifentanil was added to yield a remifentanil concentration of 50 μg/l in the experimental approach. Remifentanil and its metabolite GR90291 were measured by a modification of the HPLC electrospray ionization-tandem mass spectrometry method of Bossù *et al.*[17] Serum samples were subjected to liquid chromatography–mass spectrometry-based analysis of remifentanil and GR90291 concentrations before (blank) and 0, 30, 60, 100, and 150 min after drug application, respectively. A control run was performed for each sequence containing buffer solution instead of 0.5 ml umbilical cord blood serum.

Assay of Remifentanil. For liquid chromatography–tandem mass spectrometry analysis, the samples were transferred into plastic microvials on ice, and protein precipitation was achieved by mixing 100 μl serum with 200 μl acetonitrile; 50 μl internal standard solution (0.1% formiatic solution with a concentration of 100 μg/l of internal standard) was added. Subsequently, the vials were vortexed (Bender and Hobein, Zurich, Switzerland) for 30 s and centrifuged for 10 min at 15,800*g* and 4°C (Eppendorf centrifuge 5402; Hamburg, Germany). The supernatant was transferred into disposable glass microvials (volume 100 μl) and 10-μl samples were injected into the HPLC–tandem mass spectrometry system.

Chromatographic Conditions and Mass Spectrometry Detector Settings. Separation of sample aliquots was achieved using a BetaBasic C4 column (100 × 3.0 mm, 5 μm) with its corresponding precolumn (10 × 3.0 mm; Thermo Fisher, Dreieich, Germany). The system was equilibrated until stability of total ion current for a minimum of 1.5 h, and sensitivity was checked by analyzing an aqueous standard solution of remifentanil, metabolite, and internal standard.

The column and tray temperatures were maintained at $\upsilon = 45$°C and $\upsilon = 10$°C, respectively. The flow rate was 350 μl/min, resulting in a column pressure of 280–420 kPa. The total duration of chromatography of each sample run was 6 min. Retention times of both analytes (remifentanil and metabolite) and the internal standard were 2.04 min and 2.56 min, respectively.

Detection was carried out with a TSQ Quantum mass spectrometer (ThermoFisher, San Jose, CA), equipped with an electrospray ionization source working in positive ion and reaction monitoring mode. Instrument parameters were as

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follows: electrospray ionization source collision-induced dissociation, 10.0 V; spray voltage, 3.8 kV; nitrogen used as sheath and auxiliary gas, 45 and 10 units (arbitrary units); heated capillary temperature was set to υ = 380°C. The argon collision gas pressure was set to 1.5 mTorr.

The collision energy was set to 27 eV for remifentanil, 30 eV for GR90291, and 28 eV for internal standard, respectively. The following transitions of $[M-H]^+$ precursor ions to product ions were selected: for remifentanil, m/z 377 → 113; for GR90291, m/z 363 → 146; and for the internal standard, m/z 381 → 321.

The lower limit of quantification of remifentanil and its metabolite was 1.6 μg/l, the limit of detection was 0.32 μg/l. Linearity was demonstrated over a range of 1.6–1,000 μg/l. The intraday variability of the relative SD was 13.9% at 1.6 μg/l and 6.9% at 1,000 μg/l.

Description of the Model. Data were processed by a standard calculation program (LCQuan rev. Version 1.3; ThermoFinnigan, San Jose, CA). Corresponding data sets were imported into the pharmacokinetic program TOPFIT,[18] and Michaelis–Menten kinetics of each group were analyzed by a nonlinear compartment model based on the most appropriate model MM1IVM. The model is an integral part of TOPFIT, which is characterized by a code of as many as six characters containing the following information: MM, type of nonlinearity (Michaelis–Menten kinetics); 1, number of disposition compartments *in vitro*; IV, type of input (intravenous); M, present in the model if a metabolite is measured in addition to its parent compound. Metabolite data sets are accepted for the central compartment and parent compound data sets for the central compartment and one elimination compartment; the letter M would be absent, if only the parent compound were measured.

The model was used to fit the individual remifentanil and metabolite serum concentration-time profiles with a bolus dosage of 0.15 μg/kg remifentanil. The following parameters were investigated: half-life, Michaelis–Menten constant K_m, and elimination constant k_e.

Michaelis–Menten Equation for Biotransformation. The biotransformation of remifentanil is catalyzed by nonspecific esterases *via* hydrolysis in blood and tissues and can be represented schematically by the following closed system,

$$[A] + [E] \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} [AE] \xrightarrow{k_2} [E] + [M] + [A] \qquad (1)$$

with A = drug; E = metabolizing enzyme; [AE] = complex of drug and metabolizing enzyme; k_1 = rate constant for interaction of drug and enzyme to build a complex [AE]; k_{-1} = rate constant for dissociation of [AE] to drug and enzyme [A] + [E]; [M] = metabolite; k_2 = rate constant for dissociation of the substrate [A] and accumulation of the metabolite [M].

The differential equation describing the above model is as follows,

$$\frac{d[AE]}{dt} = k_1 \cdot [A] \cdot [E] - k_{-1} \cdot [AE] - k_2 \cdot [AE] \qquad (2)$$

The objective of the analysis is to represent the above model in terms of a Michaelis–Menten expression with the following form,

$$[AE] = [E_0] \cdot \frac{[A]}{K_m + [A]} = V_{max} \cdot \frac{c_i}{K_m + c_i} \qquad (3)$$

where

$$K_m = \frac{k_{-1}}{k_1} \qquad (4)$$

with V_{max} = maximum transfer rate; c_i = concentration (or amount) of drug in compartment i.

In nonlinear kinetics, the rate of drug transfer is not directly proportional to drug concentrations. Most commonly, nonlinear kinetics occur as a consequence of saturable (capacity-limited) transfer processes.[19] As a starting point for the current study, V_{max} was experimentally determined with independent substrate concentrations of remifentanil (50.0, 20.0, and 10.0 μg/l). V_{max} represents the total capacity of the saturable process and was calculated and fixed at 0.40 $\mu g \times l^{-1} \times min^{-1}$ for all individual calculations; K_m is equal to the value of c_i for half-maximal transfer rate and represents the affinity of the transfer system.

Statistical Analysis

The aim of this study was to analyze potential differences among the three subgroups of preterm infants (groups P1, P2, P3) and term infants (group T) concerning the activity of nonspecific blood esterases. For this purpose, we used the nonparametric Mann–Whitney test and performed pairwise comparisons for the degradation half-life of remifentanil, the ratio of the metabolite GR90291 and remifentanil after 150 min, and the Michaelis–Menten constant.

Because of the explorative character of this study, we did not adjust the significance level α = 0.05 to account for multiple testing. Therefore, all *P* values are of an explorative nature and *P* values less than 0.05 were considered to be statistically significant. All reported *P* values are two-sided, and continuous variables are presented as median ± interquartile range with minimum and maximum, respectively, in brackets. SPSS version 16.0 (SPSS 2007, Munich, Germany) was used for the statistical analysis.

Results

We analyzed umbilical cord blood samples of 34 preterm infants and six term newborns. Nine preterm infants had a

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Table 1. Kinetic Results for Every Patient

Patient	Gestational Week	$C_{remi-150}$ (nmol/l)	$C_{metab-150}$ nmol/l	Ratio M/R	$t_{1/2}$ (min)	K_m (μg/l)
1	24	57.3	85.5	1.49	190.0	107.0
2	25	42.8	64.0	1.50	124.7	84.3
3	25	70.2	94.0	1.34	182.9	101.0
4	26	50.8	78.8	1.55	118.3	65.2
5	26	48.9	67.7	1.38	124.0	73.0
6	26	61.4	95.4	1.55	139.7	83.7
7	27	51.3	89.5	1.74	134.4	71.7
8	27	57.7	86.6	1.50	178.4	107.0
9	27	62.8	82.4	1.31	220.7	126.0
10	28	55.6	83.6	1.50	153.9	96.0
11	28	52.6	90.6	1.72	146.5	119.0
12	29	40.0	95.6	2.39	123.2	104.0
13	29	35.9	83.9	2.34	145.6	84.6
14	30	31.3	74.9	2.39	143.3	97.8
15	30	28.4	67.2	2.37	123.6	82.2
16	30	29.1	68.1	2.34	137.7	88.3
17	31	26.8	78.4	2.93	97.8	67.8
18	31	32.8	68.1	2.08	134.6	89.5
19	31	29.0	58.7	2.02	146.2	105.0
20	32	41.0	108.1	2.64	113.9	68.0
21	32	39.3	99.0	2.52	110.5	72.8
22	32	45.8	110.3	2.41	155.4	84.1
23	33	58.3	127.4	2.19	143.0	85.2
24	33	47.6	103.6	2.18	101.4	74.5
25	33	31.9	120.0	3.76	76.4	51.7
26	34	50.8	103.2	2.03	193.2	183.0
27	34	38.7	83.2	2.15	107.0	70.5
28	34	50.0	70.5	1.41	168.7	119.0
29	35	34.6	63.7	1.84	102.3	74.0
30	35	40.1	88.0	2.19	166.0	121.0
31	35	35.3	32.8	0.93	145.1	84.0
32	36	42.5	82.3	1.93	151.1	123.0
33	36	35.4	78.0	2.20	120.9	99.5
34	36	31.5	68.5	2.17	128.1	109.0
35	37	39.4	82.2	2.09	119.8	71.3
36	38	49.4	67.8	1.37	207.5	121.0
37	38	45.9	66.6	1.45	158.2	95.5
38	40	45.6	60.8	1.33	182.7	109.0
39	40	45.1	71.2	1.58	193.3	110.0
40	41	50.0	64.6	1.29	206.0	116.0
Median		44.0	82.3	1.98	143.1	92.5
IQR		±15.5	±25.3	±0.81	±46.6	±34.9
Range		26.8–70.2	32.8–127.4	0.93–3.76	76.4–220.7	51.7–183.0

$C_{metab-150}$ = concentration of metabolite GR90291 after 150 min; $C_{remi-150}$ = concentration of remifentanil after 150 min; IQR = interquartile range ratio; K_m = Michaelis–Menten constant; M/R = ratio of metabolite GR90291 and remifentanil after 150 min; $t_{1/2}$ = elimination half-life.

gestational age of 24–27 weeks (group P1), 10 a gestational age of 28–31 weeks (group P2), and 15 a gestational age of 32–36 weeks (group P3). The kinetic results for each patient are displayed in table 1.

The degradation rates of remifentanil to its major metabolite GR90291 are demonstrated in figure 1. In all age groups we found a continuous degradation of remifentanil with a concomitant increase of its metabolite GR90291. However, the remifentanil concentration remained stable in control runs without serum.

The overall median degradation half-life of remifentanil was 143 ± (interquartile range) 47 min (minimum, 76 min; maximum, 221 min). The remifentanil half-life in the preterm subgroups was 140 ± 62 min (118 min; 221 min) in group P1, 141 ± 23 min (98 min; 154 min) in group P2, and 128 ± 48 min (76 min; 193 min) in group P3. These differences were of no statistical significance, although there was a tendency for a longer half-life in the most immature preterm infants of group P1 compared with more mature preterm infants in group P3 (P1 *vs.* P2, $P = 0.414$; P1 *vs.* P3, $P = 0.128$; P2 *vs.* P3, $P = 0.739$). In term infants, remifentanil half-life was 188 ± 58 min (120 min; 208 min), which was significantly longer than that of groups P2 ($P = 0.023$) and P3 ($P = 0.011$). However, half-life in term infants revealed

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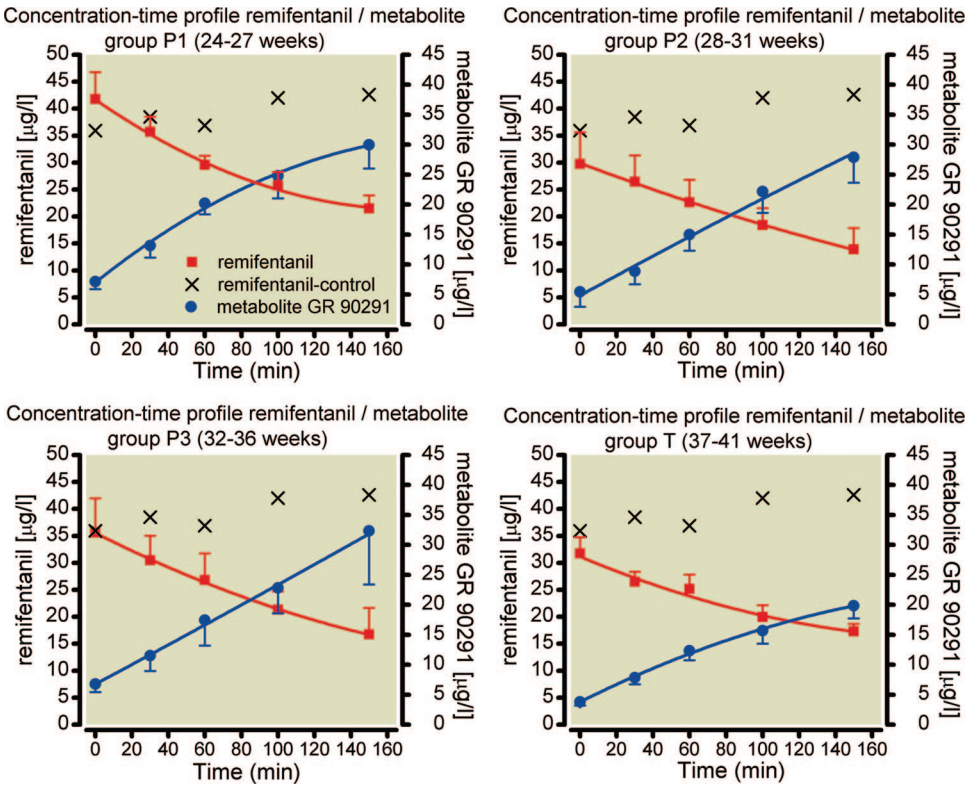

Fig. 1. Time-concentration curves of remifentanil and its metabolite GR90291 for *in vitro* metabolism in umbilical cord serum. Data are presented as mean concentration with SD. Over time there was a continuous decrease of remifentanil and an analog continuous increase of GR90291 in all age groups. In the control runs without serum remifentanil, concentrations remained stable.

no statistical difference compared with the very premature infants of group P1 ($P = 0.289$) (table 2, fig. 2).

The overall median ratio of the metabolite GR90291 and remifentanil after 150 min was 1.98 ± 0.81 (minimum, 0.93; maximum, 3.76). This ratio reflects the fraction of remifentanil metabolized to its major metabolite by unspecific esterases, and it increased in preterm infants with gestational age. The most immature infants of group P1 had a significantly lower ratio than did the more mature preterm infants of groups P2 and P3 ($P < 0.001$ and $P = 0.002$, respectively). However, term infants had a significantly lower ratio compared than did the more mature preterm infants of groups P2 and P3 ($P = 0.007$ and $P = 0.010$, respectively), but there was no significant difference between the ratios of term infants and those of the most immature preterm infants of group P1 ($P = 0.637$) (table 2, fig. 3).

Table 2. Statistical Comparisons between Groups P1, P2, P3, and T

Group Comparison	*P* Value		
	$t_{1/2}$ (min)	Ratio M/R	K_m (µg/l)
P1 *vs.* P2	0.414	0.001	0.744
P1 *vs.* P3	0.128	0.002	0.929
P1 *vs.* T	0.289	0.637	0.194
P2 *vs.* P3	0.739	0.698	0.677
P2 *vs.* T	0.023	0.007	0.159
P3 *vs.* T	0.013	0.010	0.350

K_m = Michaelis–Menten constant; ratio M/R = ratio of metabolite GR90291 and remifentanil after 150 min; $t_{1/2}$ = elimination half-life.

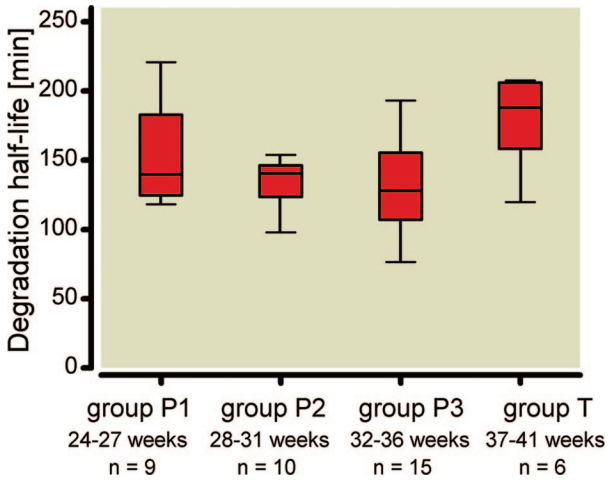

Fig. 2. *In vitro* half-life of remifentanil according to gestational age. Box plots represent median, IQR, minimum and maximum. IQR = interquartile range.

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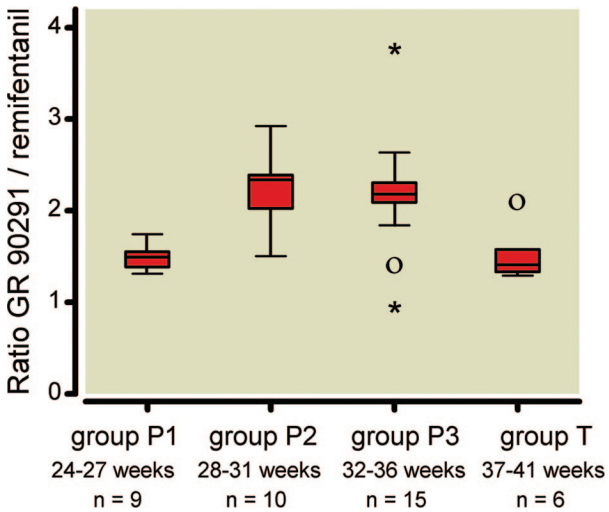

Fig. 3. Ratio of the metabolite GR90291 concentration and remifentanil concentration after 150 min according to gestational age. Box plots represent median, IQR, minimum, and maximum. Values more than 3 IQR from the box are labeled as extreme and denoted by an asterisk (*). Values more than 1.5 IQR but less than 3 IQR from the end of the box are labeled as outliers (o). IQR = interquartile range.

The overall median Michaelis–Menten constant (K_m) was 92.5 ± 34.9 μg/l (minimum, 51.7 μg/l; maximum, 183.0 μg/l). Most important, K_m was at comparable orders of magnitude in all subgroups: 84.3 ± 34.7 μg/l in group P1; 92.8 ± 20.3 μg/l in group P2; 84.1 ± 46.2 μg/l in group P3; and 109.5 ± 27.8 μg/l in group T (fig. 4). The pairwise comparisons between the groups revealed no statistical significance, and the exact *P* values are given in table 2.

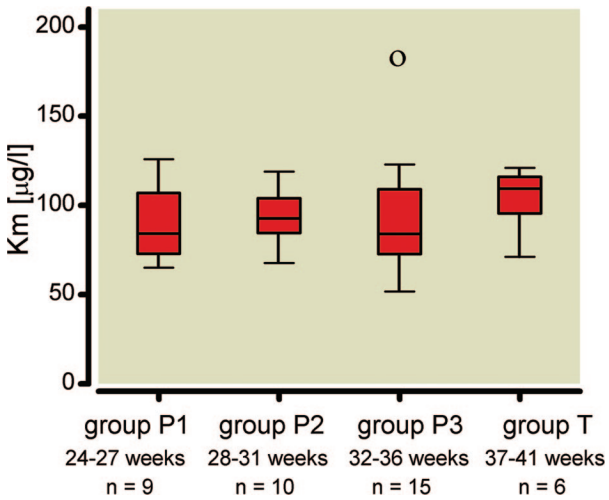

Fig. 4. Michaelis–Menten constant (K_m) according to gestational age. Box plots represent median, IQR, minimum, and maximum. Values more than 1.5 IQR but less than 3 IQR from the end of the box are labeled as outliers (o). IQR = interquartile range.

Discussion

Remifentanil is a structurally unique opioid with a short elimination half-life of approximately 5–10 min.[8] Some pharmacokinetic investigations in older children and term infants have been done, but no pharmacokinetic data exist for remifentanil in preterm infants.[13] To extend the pharmacokinetic knowledge about remifentanil in children, we analyzed the degradation of remifentanil in umbilical cord serum of preterm and term infants. Our aim was to investigate whether the activity of nonspecific blood esterases depends on gestational age.

In all gestational age groups we found a degradation of remifentanil and an inverse increase of its main metabolite GR90291 over time. In the most immature infants (less than 28 gestational weeks), the activity of nonspecific blood esterases was comparable with the activity in term infants. Spontaneous degradation of remifentanil was excluded by a control run, which revealed stable remifentanil concentrations when no serum was added to the assay.

We can only speculate concerning the increased GR90291/remifentanil ratio and the shorter half-life of remifentanil in more mature preterm infants compared with term infants. These findings may be caused by the small number of samples, with 6–15 patients per subgroup. However, these results can also reflect an increased fetal activity of nonspecific esterases compared with term infants. It is a known phenomenon that some enzymes are more active prenatally and decrease or even disappear after birth. Rarely, enzyme activity decreases throughout the last trimester of pregnancy.[20,21] The somewhat longer half-life of remifentanil in extreme preterm infants (less than 28 gestational weeks) compared with that in more mature preterm infants might be explained by these most immature infants having not yet reached their maximum enzyme activity.[22,23]

We found an *in vitro* degradation half-life of 143 min for remifentanil in umbilical cord serum of preterm and term infants. In whole blood of adults, the *in vitro* half-life of remifentanil is 37–66 min.[24] The longer remifentanil half-life in our preterm and term infants might be explained by a more mature enzyme system in adults. However, we had to analyze the activity of nonspecific esterases in serum, instead of whole blood, because we had to collect and store our samples at −80°C for later *in vitro* investigation. Therefore, another possible explanation could be an increased esterase activity in human whole blood compared with human serum caused by additional esterase activity in erythrocytes.[25] This hypothesis is supported by pharmacokinetic *in vivo* studies revealing comparable results in term infants and adults. Neonates and children younger than 2 yr exhibit a larger volume of distribution and a larger clearance than do older children or adults. The terminal elimination half-life of remifentanil in all age classes is only ~ 5 min.[7,9–11]

However, the most important finding of our study is that preterm infants of all viable gestational ages reveal a significant activity of nonspecific plasma esterases metabolizing

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remifentanil to its major metabolite GR90291. Even in extremely preterm infants we found a considerable activity of nonspecific esterases. Therefore, it seems possible that the exceptional pharmacokinetic profile of remifentanil is valid in very preterm infants.

Our *in vitro* results are limited by *in vivo* remifentanil being metabolized not only by nonspecific blood esterases, but also by nonspecific tissue esterases. For example, in dogs, approximately 11–16% of the total metabolism of remifentanil was found in muscle and intestine.[16] Therefore, our data cannot be simply transferred to the *in vivo* situation. However, clinical studies with remifentanil in preterm infants support our results because they report a short recovery profile, comparable with that seen in adults.[26,27]

We want to stress the explorative character of this study and that the reported *P* values in table 2 are not corrected for multiplicity. Because we conducted six pairwise comparisons, the global significance level of 0.05 could, for example, be corrected by using a local significance level of $0.05/6 \approx 0.008$ (Bonferroni adjustment) for each pairwise comparison. In this case, *P* values less than 0.008 would be considered statistically significant.

Nevertheless, our findings are important not only for anesthesia and analgesia of preterm infants, but also for the use of remifentanil in obstetric anesthesia. Remifentanil is known to cross the placenta with resultant respiratory depression in the neonate.[28] Our data confirm the clinical experience that the respiratory depression of the neonate resolves within a few minutes and suggest that the exceptional advantages of remifentanil might also be valid in very immature infants (less than 28 gestational weeks).[29,30]

In summary, our study demonstrates that very preterm infants have a high nonspecific esterase activity in umbilical cord blood that is comparable with that of term infants. These results support clinical experiences indicating that remifentanil is rapidly metabolized by preterm infants without prolonged side effects.

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