Comparative Pharmacokinetics and Pharmacodynamics of Remifentanil, Its Principle Metabolite (GR90291) and Alfentanil in Dogs

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ABSTRACT

Remifentanil is an esterase-metabolized opioid developed for use in anesthesia. The principal metabolite of remifentanil, GR90291, is considered to be less potent. This study determined the relative potency of GR90291 and alfentanil, compared with remifentanil, in anesthetized dogs. Male dogs received thiamylal sodium, and anesthesia was maintained using isoflurane and N₂O in oxygen. Each dog received a 5-min infusion of 0.5 mg/kg/min remifentanil, 500 μg/kg/min GR90291 and 1.6 mg/kg/min alfentanil in random order, separated by 1 week. Serial blood samples were collected during and after the infusion. The electroencephalogram was evaluated using apneic analysis. The pharmacokinetics and pharmacodynamics of remifentanil, GR90291 and alfentanil were determined using non-linear least-squares regression analysis. Remifentanil was rapidly eliminated, with a terminal half-life of 6 min, compared with 19 min for GR90291 and alfentanil. Using the estimated concentration that elicits 50% of the maximum response (EC₅₀) for delta EEG activity and spectral edge 95, remifentanil was 4213 to 4637 times more potent than GR90291 and 7.7 to 8.5 times more potent than alfentanil. The blood-brain equilibration half-life was 2.3 to 5.2 min for remifentanil, 0.39 to 0.41 min for GR90291 and 3.1 to 3.7 min for alfentanil.

Materials and Methods

Study design. This study was approved by the institutional review board for animal research at the University of Illinois at Chicago. Male purpose-bred mongrel dogs (26.0–34.5 kg) were housed under a 12-hr light/dark cycle, with access to food once each day and with water available ad libitum. Dogs received i.v. thiamylal sodium (35 mg/kg), and anesthesia was initiated with 2% isoflurane and 50% nitrous oxide in oxygen after endotracheal intubation. Neuromuscular blockade was achieved using vecuronium (0.01 mg/kg/hr i.v.). A

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ABBREVIATIONS: EEG, electroencephalogram; kₑ₀, blood-brain equilibration rate constant.

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rectal thermistor probe was used to monitor body temperature, which was maintained at 40 ± 1°C. On the first treatment day, chronically indwelling catheters were implanted in the femoral artery and vein. The catheters were guided s.c. to the dog’s back and externalized through a small incision. After instrumentation was completed, the end-tidal isoflurane concentration, measured using a Datex anesthetic analyzer (Datex, Helsinki, Finland), was adjusted to 1% (0.7 minimum alveolar concentration) with 50% nitrous oxide in oxygen. Dogs were allowed to stabilize for a minimum of 30 min before infusion of study drugs. Blood gases were measured every 30 min, and end-tidal CO2 was maintained constant (pACO2, 35–40 mm Hg). On the subsequent treatment days, the same anesthetic protocol was followed.

Bipolar needle electrodes were placed bilaterally in the skin for parieto-temporal EEG recording using a Life Scan monitor (Neuro- metrics, San Diego, CA). This system extracts the wave, frequency and amplitude information from the EEG waveform using aperiodic analysis. A squared function of the electrical amplitude was determined within each of the following frequency bands: 0.5 to 3 Hz (delta waves), 3.1 to 8 Hz (theta waves), 8.1 to 12 Hz (alpha waves) and 12.1 to 30 Hz (beta waves). The fraction of activity of each band in relation to the total electrical activity was determined. Data were averaged over 1-min epochs. Spectral edge95 was calculated as the frequency below which 95% of the EEG power was contained, and delta EEG activity was determined as the total energy contained within the delta frequency band (Scott et al., 1991; Hoffman et al., 1993). The EEG waveform was allowed to stabilize in each dog before administration of study drugs. As a result of technical difficulties, EEG data were not available for all drug treatments in some dogs. Table 1 lists the dogs and drug treatments for which EEG data were available for pharmacodynamic evaluation.

Each dog received a 5-min infusion of one of three treatments, i.e., 0.5 μg/kg/min remifentanil, 500 μg/kg/min GR90291 or 1.6 mg/kg/min alfentanil. These treatments were given in random order and separated by 1-week intervals. The doses of remifentanil (Salmenpera et al., 1992) and alfentanil (Hall et al., 1994) have been shown to reduce enflurane minimum alveolar concentration by 50% in dogs. Alfentanil was infused as a comparator agent for assessing the reliability of the EEG analysis in estimating the relative potencies of GR90291 and remifentanil. The dose of GR90291 was chosen to be comparable to the dose of remifentanil, based on a 1/100th relative potency from the previous animal models. Arterial blood samples (5 ml) were collected before the start of the infusion (0 min) and every 1 min during the infusion (1–5 min). After the infusion, samples were collected every 1 min for 5 min (6–10 min), every 2 min for an additional 10 min (11–20 min) and then at 25 min after infusion (30 min).

Remifentanil blood samples required special sample processing because of the potential for continued hydrolysis after sample collection. Blood samples were immediately added to a sample tube containing 50% citric acid solution for stabilization, mixed and stored frozen until analysis. Before bioanalysis, samples were mixed with acetonitrile and centrifuged, and 0.1 M sodium acetate buffer, pH 6, was added to the supernatant. Samples were then loaded onto conditioned solid-phase extraction columns (Bond Elut Certify; Varian, Harbor City, CA) and rinsed with acetic acid and 2-propanol. Remifentanil was eluted with 2% ammonium hydroxide solution in ethyl acetate, evaporated to dryness and reconstituted in ethyl acetate. Concentrations were determined using a validated gas chromatography/mass spectrometry/selected ion-monitoring method (Grosse et al., 1994). The quantitation limit was 0.1 ng/ml and the interassay coefficient of variation was <16%. Bioanalysis of GR90291 was not performed for samples collected after administration of remifentanil.

GR90291 concentrations were determined using high-performance liquid chromatography (Glaxo Wellcome Inc., data on file). Plasma was loaded onto a conditioned solid-phase extraction column (C18 Bond Elut; Varian), rinsed with water and acetonitrile and then eluted with acetonitrile/phosphate buffer, pH 4.0 (1:4). The high-performance liquid chromatography system consisted of a Supelcosil LC-1 column (Supelco, Inc., Bellefonte, PA), a mobile phase of 15% acetonitrile in 0.05 M phosphate buffer, pH 3, and UV detection at 210 nm. The lower limit of quantitation was 100 ng/ml, with an interassay coefficient of variation of <13%.

Alfentanil blood samples were mixed with 0.2 M zinc sulfate and centrifuged, and 0.1 M sodium acetate buffer, pH 6, was added to the supernatant. Samples were then loaded onto conditioned solid-phase extraction columns (Bond Elut Certify; Varian) and rinsed with acetic acid and methanol. Alfentanil was eluted with 2% ammonium hydroxide solution in ethyl acetate, evaporated to dryness and reconstituted in ethyl acetate. Concentrations were determined using a gas chromatography/mass spectrometry/selected ion-monitoring method (Jersey et al., 1993). The limit of quantitation was 1 ng/ml, and the interassay coefficient of variation was <10%.

**Pharmacokinetics and pharmacodynamics.** The pharmacokinetics and pharmacodynamics of remifentanil, GR90291 and alfentanil were determined in each dog using nonlinear, least-squares, regression analysis (PCNONLIN 4.2; SCI Software, Lexington, KY). A two-compartment, zero-order, infusion model was used to describe the concentration-time profiles of each compound. The modeling procedure was conducted using weighting of 1/Y² or 1/Y³ or no weighting, as appropriate, where Y is the predicted value for concentration or EEG. Pharmacokinetic and pharmacodynamic model selection was based on inspection of residual plots, the observed and predicted concentration-time and effect-time profiles and the Akaike information criterion (Boxenbaum et al., 1974; Yamaoka et al., 1978). The central compartment volume of distribution, elimination rate constant (k₁₀) and distribution rate constants (k₁₂ and k₂₁) were estimated from the pharmacokinetic modeling. Clearance, steady-state volume of distribution and terminal half-life were then obtained using standard techniques (Gibaldi and Perrier, 1982).

A two-step procedure was used to characterize the pharmacokinetic/pharmacodynamic relationship for each study drug. First, the pharmacokinetic parameters for remifentanil, GR90291 and alfentanil were estimated. Second, the pharmacokinetic parameters were fixed to the value of the estimates and the pharmacodynamic parameters were estimated using a rate constant (kₚ₀) that characterizes the temporal aspects between drug concentration and effect (Sheiner et al., 1979). The equilibration half-life was estimated as ln(2)/kₚ₀. For interested readers, excellent reviews of effect-compartment modeling and discussion of certain assumptions required by the model are provided by Holford and Sheiner (1981, 1982). The technique of effect compartment modeling has been previously used to assess the relationship between remifentanil concentrations and changes in the EEG waveform in healthy volunteers (Egan et al., 1994a).
The EEG effects of each drug were evaluated using a sigmoid $E_{\text{max}}$ model (Holford and Sheiner, 1982),

$$EEG \text{ activity} = E_0 + \frac{E_{\text{max}} \cdot C_e \gamma}{C_e + EC_{50} \gamma}$$  \hspace{1cm} (1)\

where $E_0$ is the base-line EEG activity, $E_{\text{max}}$ is the maximum EEG effect, $EC_{50}$ is the effect site concentration that elicits 50% of the maximum response, $\gamma$ is the sigmoidicity factor and $C_e$ is the concentration of drug at the effect site. The EEG effect of GR90291 after the remifentanil infusion was assumed to be negligible, based on previous pharmacokinetic and relative potency estimates (Glaxo Wellcome Inc., data on file).

Delta EEG activity was modeled as an increase from base line, and spectral edge$_{95}$ was modeled as a reduction from base line. The potency ratios and corresponding 90% confidence intervals for remifentanil/GR90291 and remifentanil/alfentanil were estimated after logarithmic transformation of the $EC_{50}$ values (SAS version 6.07; SAS, Cary, NC). All pharmacokinetic and pharmacodynamic parameters were presented as mean and S.D., except half-life, which was expressed as harmonic mean and jackknife S.D. (Lam et al., 1985).

Results

The concentration-time profiles of remifentanil, GR90291 and alfentanil (fig. 1) were well described by a two-compartment pharmacokinetic model. Table 2 shows a summary of the pharmacokinetic parameters for remifentanil, GR90291 and alfentanil. The mean clearance of remifentanil was 6 times greater than that of its metabolite GR90291 and 2 times greater than that of alfentanil in dogs. The mean central compartment volume of distribution was similar for remifentanil, GR90291 and alfentanil; however, the mean steady-state volume of distribution of alfentanil was larger than those of remifentanil and GR90291. The rapid elimination of remifentanil was evident from the short terminal half-life (5.59 min), compared with those of GR90291 (19.2 min) and alfentanil (19.9 min).

The time course of the changes in EEG effect closely correlated with the changes in drug concentration. An illustration of the overall blood concentration-EEG effect time course within individual dogs receiving remifentanil (fig. 2A), GR90291 (fig. 2B) and alfentanil (fig. 2C) is shown in figure 2. The profiles show the rapid onset and termination of effect with increasing drug concentration, particularly for GR90291. The blood concentration-delta EEG activity profile showed counterclockwise hysteresis, indicative of a temporal dissociation between the concentration of drug in the blood and the effect site. Using the same dogs depicted in figure 2, the relationship between blood concentration and delta wave activity (hysteresis) for remifentanil, alfentanil and GR90291 is shown in figure 3 (top). For comparison, the hysteresis profiles were plotted on a logarithmic scale, with EEG effect expressed as percentage of maximum effect. The temporal delay between blood concentration and effect was accommodated using $k_{e0}$ to predict effect site concentrations, thereby eliminating the hysteresis (fig. 3, bottom). Although not shown graphically, the hysteresis and collapsed hysteresis profiles were similar for spectral edge$_{95}$.

The pharmacodynamic parameters for delta EEG activity and spectral edge$_{95}$ are listed in table 3. Estimates of $\gamma$ were typically >3, indicative of a steep sigmoidal relationship between effect site concentrations and EEG effect. The mean equilibration half-life for GR90291 (0.39–0.41 min) was smaller than those for remifentanil (2.3–5.2 min) and alfentanil (3.1–3.7 min). Owing to differences in electrode place-
ment and contact impedance, raw base-line EEG signal strength varied between dogs and between treatments within dogs. This is observed in the variability of $E_{\text{max}}$ and $E_{\text{50}}$ (table 3). Accordingly, for graphical presentation of the three study treatments, the data were presented as a percentage of the maximum EEG effect. Figure 4 shows the effect site concentration vs. delta wave activity, and associated mean $E_{\text{50}}$ and S.D., for remifentanil, GR90291 and alfentanil. Between each treatment group, the profiles show good consistency in response to the EEG effects of these opioid derivatives.

Using delta EEG activity, the $E_{\text{50}}$ values for remifentanil, GR90291 and alfentanil in the presence of 50% $N_2O$ and 1% isoflurane anesthesia were 0.97, 4515 and 7.70 ng/ml, respectively. Using spectral edge 95, the $E_{\text{50}}$ values for remifentanil, GR90291 and alfentanil in the presence of 50% $N_2O$ and 1% isoflurane anesthesia were 0.64, 2930 and 5.00 ng/ml, respectively. The relative potencies, with corresponding 90% confidence intervals, of GR90291 and alfentanil, compared with remifentanil, are presented in table 4. For descriptive purposes, the potencies of GR90291 and alfentanil are presented relative to a remifentanil potency of unity. Compared with remifentanil, its principle metabolite GR90291 was approximately 1/8th as potent.

**Opioid derivatives produce a characteristic slowing of the EEG waveform, i.e., formation of delta waves.** These EEG changes were used in this study to determine the in vivo relative potency of the principle metabolite of remifentanil, GR90291. Alfentanil was used as a comparator for assessing the reliability of the EEG analysis in estimating the relative potencies of GR90291 and remifentanil. The concentrations of each compound were modeled to characterize the concentration-time profile during the EEG measurement time period. This allowed predicted concentrations to be used in the comparative assessment of the pharmacodynamics of remifentanil, GR90291 and alfentanil.

**TABLE 2**

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter</th>
<th>Remifentanil ($n = 7$)</th>
<th>GR90291 ($n = 8$)</th>
<th>Alfentanil ($n = 9$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V_c$ (ml/kg)$^a$</td>
<td>117 ± 60</td>
<td>135 ± 60</td>
<td>132 ± 41</td>
</tr>
<tr>
<td>$V_{ssp}$ (ml/kg)</td>
<td>222 ± 102</td>
<td>293 ± 130</td>
<td>558 ± 230</td>
</tr>
<tr>
<td>$CL$ (ml/min/kg)</td>
<td>63.1 ± 18.1</td>
<td>10.6 ± 3.90</td>
<td>29.8 ± 14.5</td>
</tr>
<tr>
<td>$T_{1/2}$ (min)$^b$</td>
<td>5.59 ± 0.62</td>
<td>19.2 ± 9.63</td>
<td>19.9 ± 9.21</td>
</tr>
<tr>
<td>$K_{10}$ (min$^{-1}$)</td>
<td>0.5856 ± 0.1481</td>
<td>0.0853 ± 0.0324</td>
<td>0.2235 ± 0.0663</td>
</tr>
<tr>
<td>$K_{12}$ (min$^{-1}$)</td>
<td>0.1569 ± 0.0467</td>
<td>0.1761 ± 0.0790</td>
<td>0.2076 ± 0.0563</td>
</tr>
<tr>
<td>$K_{21}$ (min$^{-1}$)</td>
<td>0.1676 ± 0.0219</td>
<td>0.1412 ± 0.0731</td>
<td>0.0711 ± 0.0243</td>
</tr>
</tbody>
</table>

$^a V_c$, central compartment volume; $V_{ssp}$, steady-state volume of distribution; $CL$, clearance.

$^b$ Values expressed as harmonic mean and jackknife S.D. (Lam et al., 1985).

times more rapid than that of GR90291 and 4 times more rapid than that of alfentanil (Westmoreland et al., 1993; Egan et al., 1994b).

Based on in vivo and in vitro animal models, GR90291 was previously estimated to have 1/300th to 1/1000th the activity of remifentanil (James, 1994). For this reason, GR90291 was infused in the dogs at 1000 times the infusion dose of remifentanil, to determine an in vivo potency ratio. Alfentanil was previously shown to be approximately 20 to 30 times less potent than remifentanil using analgesic and respiratory effects (Glass et al., 1993) and 17 times less potent using EEG spectral edge 95 (Egan et al., 1994a), comparing equipotent concentrations of the drugs in the blood. Because of the differences in pharmacokinetics of remifentanil, GR90291 and alfentanil, the evaluation of relative potency was based on $E_{\text{50}}$ rather than dose.

As previously noted (Bovill et al., 1983; Scott et al., 1985, 1991), the EEG proved to be a sensitive and reliable measure of opioid activity. The characteristic slowing of the EEG waveform was evident during the infusion of each study drug. Profiles of the blood concentration vs. EEG activity revealed hysteresis, indicative of the equilibration delay between the concentration of drug in the blood and the concentration of drug at the effect site. Using the methodology developed by Hull et al. (1978) and Sheiner et al. (1979), a pharmacokinetic/pharmacodynamic model was used to describe the relationship between the drug concentration and EEG effects.

The concentration-effect profiles for each drug were adequately described using a sigmoidal $E_{\text{max}}$ pharmacodynamic model, which allowed estimation of the effect site concentration necessary to achieve 50% of the maximum response ($E_{\text{50}}$). The $E_{\text{50}}$ values were then used for evaluating the relative potencies of GR90291 and alfentanil, compared with remifentanil.

Visual inspection of the hysteresis and collapsed hysteresis plots showed good distribution of observed EEG data about the fitted line. In some instances, the predicted profiles appeared to over- or underestimate base-line EEG and data collected shortly after initiation of the infusion. This can be explained by inspection of the EEG time course profiles (fig. 2). Note that the base line is estimated not only from EEG data collected before and shortly after initiation of the infusion but also from a preponderance of EEG data collected after the infusion, when the response measure had returned to base line. The value of $\gamma$ (sigmoidicity $> 3$) indicated a steep relationship between drug concentration and effect. This is also evident from the collapsed hysteresis profiles (fig. 3, bottom).

**Discussion**

The pharmacokinetics of remifentanil, GR90291 and alfentanil were well described using a two-compartment i.v. infusion model. Remifentanil was rapidly eliminated, with a terminal half-life of 5.59 min, which is consistent with previous studies in dogs ($T_{1/2}$, 4–8 min) (Feldman et al., 1991). GR90291 and alfentanil were eliminated 3.5 times more slowly, with half-life values of 19 to 20 min. These results are consistent with previous studies in human volunteers, where the half-life of remifentanil was shown to be about 5 to 8
As indicated by the estimates for $k_{eq}$, the blood-brain equilibration half-life of GR90291 (0.39–0.41 min) with the hypothetical effect site was almost 10 times faster than those of remifentanil (2.3–5.2 min) and alfentanil (3.1–3.7 min). In pharmacokinetics, a rate constant ($k$) is a function of clearance ($CL$) (milliliters per minute) and volume ($V$) (milliliters). For a given drug, and assuming constant clearance, the time required to achieve steady state (equilibrium) would be greater as volume increases ($k = CL/V$). That is, the drug would equilibrate faster with a small volume, as opposed to a large volume. An analogous argument can be constructed using techniques established for physiological modeling (Bernareggi and Rowland, 1991). A rate constant ($k$) can be

Fig. 2. Typical individual time course profiles of the observed and predicted blood concentrations and EEG delta wave activity during and after infusions of remifentanil (A), GR90291 (B) and alfentanil (C). ●, drug concentrations; ○, delta activity.

Fig. 3. Profiles of the relationships between blood concentration and delta wave activity (hysteresis) (top) and predicted effect site concentration and delta wave activity (collapsed hysteresis) (bottom) during and after infusions of remifentanil (REMI), alfentanil (ALFEN) and GR90291. Top, arrows, direction in time. For clarity, the observed blood concentrations of remifentanil, alfentanil and GR90291 are not shown in the top. Delta wave activity is expressed as percentage of $E_{max}$ and concentration is expressed on a logarithmic scale for comparison of the three compounds.
Relative potencies of GR90291 and alfentanil, compared with remifentanil, using EC50 for delta EEG activity and spectral edge95

<table>
<thead>
<tr>
<th>Pharmacodynamic Measure</th>
<th>Remifentanil:GR90291</th>
<th>Remifentanil:Alfentanil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delta EEG (ng/ml)</td>
<td>1:4637 (1:3156, 1:6814)</td>
<td>8:5 (1:5.8, 1:12.3)</td>
</tr>
<tr>
<td>Spectral edge95 (ng/ml)</td>
<td>1:4213 (1:2331, 1:7616)</td>
<td>1:7.7 (1:4.4, 1:13.8)</td>
</tr>
</tbody>
</table>

* Potency is represented relative to an EC50 of 1 ng/ml for remifentanil.

TABLE 4

Mean ± SD pharmacodynamic parameters for remifentanil, GR90291 and alfentanil in anesthetized dogs

<table>
<thead>
<tr>
<th>Pharmacodynamic Parameter</th>
<th>Remifentanil (n = 7)</th>
<th>GR90291 (n = 8)</th>
<th>Alfentanil (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>E0</td>
<td>247 ± 271</td>
<td>276 ± 492</td>
<td>1563 ± 3379</td>
</tr>
<tr>
<td>Delta EEG</td>
<td>15 ± 2.7</td>
<td>16 ± 3.8</td>
<td>14 ± 3.9</td>
</tr>
<tr>
<td>Spectral edge95</td>
<td>3325 ± 3352</td>
<td>2628 ± 3224</td>
<td>2801 ± 4114</td>
</tr>
<tr>
<td>T1/2 (min)</td>
<td>10 ± 2.5</td>
<td>15 ± 6.1</td>
<td>10 ± 5.5</td>
</tr>
<tr>
<td>Delta EEG</td>
<td>3.6 ± 2.7</td>
<td>8.3 ± 10.3</td>
<td>4.0 ± 3.1</td>
</tr>
<tr>
<td>Spectral edge95</td>
<td>20 ± 33</td>
<td>9.3 ± 7.6</td>
<td>31 ± 53</td>
</tr>
<tr>
<td>EC50 (ng/ml)</td>
<td>0.97 ± 0.41</td>
<td>4515 ± 1876</td>
<td>7.70 ± 4.27</td>
</tr>
<tr>
<td>Delta EEG</td>
<td>0.64 ± 0.18</td>
<td>2930 ± 2415</td>
<td>5.00 ± 2.48</td>
</tr>
<tr>
<td>Spectral edge95</td>
<td>5.2 ± 6.4</td>
<td>0.41 ± 1.09</td>
<td>3.7 ± 2.2</td>
</tr>
</tbody>
</table>

* Remifentanil, n = 6; GR90291, n = 7; alfentanil, n = 8.

An evaluation of k<sub>α0</sub> can be proposed for each study drug using the above relationship. Assuming that blood flow and volume remain constant for a given dog in a crossover study design, k<sub>α0</sub> can be expressed as an inverse relationship of the ability of a drug to partition into a compartment (e.g., brain), described in terms of flow (Q) (milliliters per minute), volume (V) (milliliters) and the partition coefficient of the drug (K<sub>p</sub>),

\[ k = \frac{Q}{V} \frac{1}{K_p} \]  

Considering the chemical structure of GR90291, relative to remifentanil and alfentanil, it is likely that the polarity of this carboxylic acid metabolite is greater than that of the parent ester and alfentanil, and thus the partition coefficient of GR90291 is much smaller. Therefore, the rate of penetration (or equilibration) for GR90291 would be expected to be faster than that for remifentanil and alfentanil, leading to a smaller equilibration half-life \([k_{α0} T_{1/2} = \ln(2)/k_{α0}].\) On the other hand, the extent of penetration of GR90291 would be expected to be lower than that of remifentanil and alfentanil. These arguments are similar to those discussed for the estimate of \(k_{αd}\) for d-tubocurarine (Sheiner et al., 1979).

Within each dog, the EC50 values for remifentanil, GR90291 and alfentanil using delta EEG activity were typically higher than those estimated using spectral edge95, emphasizing the need to compare “like with like” pharmacodynamic response measures. The EC50 obtained from delta EEG activity was about 1.5 times higher than that estimated using spectral edge95. Using the EC50 values for remifentanil and GR90291, potencies of 1:4637 for delta EEG activity and 1:4213 for spectral edge95 were obtained. Similarly, remifentanil to alfentanil potencies of 1:8.5 and 1:7.7 were obtained for delta EEG activity and spectral edge95, respectively. These potency ratios indicate that the principle remifentanil metabolite, GR90291, possesses about 1/4600th the potency of remifentanil and that alfentanil is approximately 1/8th as potent as remifentanil.

Accurate knowledge of the relative potency of GR90291 was important to assess the significance of its accumulation in humans. Because the primary route of elimination of remifentanil is by the kidneys and because GR90291 shows a potency that is 4600 times less than that of remifentanil, the opioid effects of GR90291 may assume importance only during prolonged, high-dose infusions of remifentanil in anephric patients.

References


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