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Pharmacokinetic–Pharmacodynamic Modeling of Opioids

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Abstract
The effects of opioids usually parallel the plasma concentrations but with a temporal shift. This temporal shift differs between opioids. It is small with alfentanil or remifentanil and very long with the active metabolite of morphine, morphine-6-glucuronide (M6G). The mathematical and experimental techniques for modeling these pharmacokinetic-pharmacodynamic (PK/PD) relationships were developed in the late 1970s. The delay between plasma concentrations and effects is accounted for by the introduction of a hypothetic effect compartment, which is linked to the plasma compartment by a first-order transfer function with a rate constant ke0. The effects are then linked to the concentrations at effects site by standard pharmacodynamic models such as sigmoid (“Emax”) models or power models, depending on the actual effect measure. These principles were first applied to the opioids fentanyl and alfentanil in 1985. Since then, PK/PD of opioids have been repeatedly assessed, using EEG derived parameters, pupil size, and experimental and clinical pain as effect measures. The opioids of the fentanyl group, methadone, morphine, and piritramid, are today well characterized with respect to their PK/PD properties. Alfentanil and remifentanil are very fast equilibrating opioids with equilibration half-lives between plasma and effect site of about 1 minute. They are followed by fentanyl and sufentanil, each with equilibration half-lives of about 6 min. Methadone equilibrates with a half-life of about 8 min. Morphine, in contrast, equilibrates with a half-life of 2–3 h. The slowest opioid with respect to plasma-effect site transfer is M6G, with an equilibration half-life of about 7 h. PK/PD modeling has advanced the understanding of the time course of the clinical effects of opioids after various dosing regimens. It may provide a rational basis for the selection of opioids in clinical circumstances. PK/PD modeling of opioids may also be employed for the design and the interpretation of experiments addressing clinical effects of opioids. J Pain Symptom Manage 2005;29:S90–S103. © 2005 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.

Key Words
Concentration-response relationship, pain therapy, population modeling, effect compartment

Introduction
Different dosing regimens of opioids may result in different time courses of the opioid plasma concentrations, which in turn lead to different time courses of opioid effects. A bolus
injection is used when an immediate or a short-term effect is desired. Intravenous infusions, sustained release tablets, or transdermal delivery systems are used when long-term effects are intended. The clinical observation of the effects paralleling the plasma concentration is apparently supported by the reports of a good correlation between plasma concentrations of methadone and its clinical effects.\(^1,2\)

Opioids differ with respect to the correlation between plasma concentrations and effects. The effects of fentanyl and alfentanil apparently parallel the plasma concentrations more closely than those of morphine and meperidine. When injecting a bolus of 10 mg morphine, the opioid effects increase during the first hour, although plasma concentrations have their maximum immediately after the injection is finished. Thus, at least for some opioids, there appears to be a delay between the time-course of the plasma concentrations and the time course of the effects.

A clinical case will illustrate this delay between plasma concentration and effects. A 22-year-old man with Goodpasture syndrome, end-stage renal disease, and severe arterial hypertension underwent bilateral nephrectomy.\(^3\) He received 40 mg and 30 mg of morphine, respectively, as the sole analgesic at the beginning and at the end of a 3.5-h surgery (intravenous bolus injections). Postoperative patient-controlled analgesia (PCA) using morphine was begun. The patient indicated mild pain at rest and severe pain when moving. He self-administered 36 mg of intravenous morphine during the first 18 h after surgery and another 4 mg during the following 13 h. He became unconscious 31 h after surgery and remained in that state for 45 h. This time course was also reflected by the results of vigilance tests administered in the postoperative period (Galveston orientation and amnesia test\(^4\), digital span test assessing how many ciphers can be repeated correctly, and reaction time to a visual stimulus). The patient underwent hemodialysis at 45 h, 88 h, and 162 h after surgery. He was unconscious during the first hemodialysis and remained in that state for 45 h. This time course was also reflected by the results of vigilance tests administered in the postoperative period (Galveston orientation and amnesia test\(^4\), digital span test assessing how many ciphers can be repeated correctly, and reaction time to a visual stimulus). The patient underwent hemodialysis at 45 h, 88 h, and 162 h after surgery. He was unconscious during the first hemodialysis and remained in that state for 34 h thereafter. Blood samples were drawn in the pre- and postoperative period to assay for plasma concentrations of morphine and its glucuronide metabolites using high performance liquid chromatography.\(^5\) When the patient became unconscious 31 h after surgery, the morphine plasma concentration had been below the lower limit of quantification of 25 ng/mL for more than 26 h.\(^5\) M6G concentrations had already been close to their maximum for 26 h. The hemodialysis starting 45 h after surgery almost completely cleared M6G from plasma. However, the patient did not regain consciousness until 34 h after hemodialysis (Figure 1).

This case illustrates that, in the setting of renal insufficiency, severe opioid side effects can occur many hours after morphine plasma concentrations have peaked and M6G concentrations have reached a plateau in plasma. These side effects are most likely mediated by M6G and not by morphine or morphine-3-glucuronide (M3G). The main morphine metabolite M3G does not exert depressant effects in the CNS.\(^6\) Morphine itself equilibrates too quickly from blood into the brain to account for observed delay of many hours between the plasma concentration versus time profile and the effect versus time profile, respectively. Despite two large intravenous doses of morphine during surgery, the patient experienced postoperative pain and continued to self-administer morphine by PCA. At this time, the high plasma concentrations of M6G did not seem to result in clinically relevant analgesia. However, with a delay of many hours, similar plasma concentrations of M6G resulted in toxic side effects, i.e., the patient became unconscious. As the slow transfer between plasma and effect compartment is the reason for the delayed appearance of opioid side effects, it is also likely to be the reason why the patient remained unconscious for a long period after M6G had disappeared from plasma. Despite its elimination from plasma, it was probably still present at the effect site at high enough concentrations to maintain clinical opioid effects.

Monitoring of morphine concentrations plasma in the present clinical case would not have given any indication for upcoming severe opioid side effects. Even monitoring of M6G plasma concentrations would not necessarily have led to the conclusion of toxicity because M6G levels were high for a long time without clinical effects. The time course of the opioid symptoms can only be explained when assuming that M6G very slowly equilibrates between plasma and the central nervous system. This
Fig. 1. For bilateral nephrectomy, a total amount of 110 mg of intravenous morphine had been given to a young man with chronic severe renal failure. Unconsciousness started at a time when morphine was no longer detectable in plasma, and M6G concentrations had been high for more than a day. Hemodialysis starting 45 h after surgery almost completely cleared M6G from plasma. However, the patient remained unconscious for another 34 h. The slow equilibration of M6G between plasma and the brain seems to explain the long delay between reaching high plasma concentrations of M6G and the onset of unconsciousness, as well as the slow recovery from unconsciousness after clearing most M6G from plasma with hemodialysis. The time course of morphine dosage, the plasma concentrations of morphine, M6G, and M3G is displayed. From Angst et al.  

reasoning underscores the rationale for PK/PD modeling.

**Principles of PK/PD Modeling**

The principles of PK/PD modeling were developed in the late 1970s. PK/PD modeling links effects to the concentrations of an opioid. The effects depend on the concentrations at the site of effects, for example, the CNS, which the opioid may reach with some difficulty. An important application of PK/PD modeling is, therefore, to account for the delay between the time courses of the plasma concentrations and that of the effects as were observed in the above-mentioned case.

The major points of so-called “indirect link” PK/PD modeling start with the plasma concentration versus time profile of the opioid, to which the concentration versus time profile at the effect site can be linked via the concept of an effect site. Dose response relationships of analgesics have been elsewhere reviewed, with a broader inclusion of non-modeling studies in addition to PK/PD modeling approaches.

An opioid’s disposition can be regarded as monotonically decreasing curve that can be described by a sum of exponentials

\[
C_i(t) = \sum_{i=1}^{n} A_i e^{-\lambda_i t}
\]  

(1)
where \( C_p(t) \) denotes the concentration versus time profile after an intravenous dose \( D_{iv} \). The corresponding unit impulse response of the system is given by

\[
f_{b}(t) = \frac{C_p(t)}{D_{iv}} = \sum_{i=1}^{\infty} \alpha_i e^{-\lambda_i t},
\]

where \( \alpha_i = A_i / D_{iv} \).

The concentration versus time profiles is governed by the unit impulse response (equation 2) and by the specific dosing schedule by which the opioid is administered. For a bolus injection, the input function, \( I(t) \), is \( \text{Dose} \cdot \text{Dirac}(t) \), \( \text{Dirac}(t) \) being a function that has a value of 1 when the term in the parentheses equals zero (i.e., when \( t = 0 \)), and a value of zero otherwise. For an intravenous infusion, \( I(t) = k_0 \cdot \text{Heaviside}(t-T_{\text{start}}) \cdot \text{Heaviside}(t-T_{\text{end}}) \), where \( T_{\text{start}} \) is the time of the start of the infusion, \( T_{\text{end}} \) the time of the end of the infusion, \( k_0 \) the constant rate of the infusion, and \( \text{Heaviside} \) is a step function that has a value of 1 when the term in the parentheses is greater than zero, and a value of zero if the term in the parentheses is smaller than zero.

The plasma concentration versus time curve, \( C_p(t) \), of a drug can be regarded as a convolution of the input or dosing function, \( I(t) \), and the disposition function \( f_{b}(t) \)

\[
C_p(t) = I(t) * f_{b}(t),
\]

where \( f_{b}(t) \) is given by equation 2, and the asterisk means “convolution.” For example, the plasma concentration versus time profile for a drug with three-compartment disposition after bolus injection is

\[
C_p(t) = \text{Dose} \cdot (\alpha_1 \cdot e^{-\lambda_1 t} + \alpha_2 \cdot e^{-\lambda_2 t} + \alpha_3 \cdot e^{-\lambda_3 t})
\]

To account for the delay between the time courses of the plasma concentrations and the time course of the effects, an effect compartment with an equilibration time constant \( k_{\text{el}} \) between plasma concentrations and effect is introduced into the model. The concentrations at effect site, \( C_e(t) \), are obtained by convolution of the plasma concentration versus time profile, \( C_p(t) \), with a transfer function, \( f_{r}(t) \). A first-order function has been used in most cases

\[
f_{r}(t) = k_{\text{el}} \cdot e^{-k_{\text{el}} t}
\]

The half-life, \( t_{1/2,\text{el}} \), of this first-order transfer is given by \( \ln(2)/k_{\text{el}} \). The concentrations at effect site, \( C_e(t) \), are thus

\[
C_e(t) = C_p(t) \cdot f_{r}(t) = k_{\text{el}} \cdot e^{-k_{\text{el}} t} \cdot C_p(t)
\]

where the asterisk denotes “convolution.”

To the concentrations at the site of effect, the effect \( E \) is linked by a pharmacodynamic model. This is often a sigmoid model of

\[
E = E_0 + \frac{E_{\text{max}} C_e^\gamma}{E_{50} + C_e^\gamma}
\]

where \( E_0 \) is the baseline value of the effects measure, \( E_{\text{max}} \) the maximum possible effect, \( E_{50} \) the concentration at effect site that leads to a half-maximum effect, and \( \gamma \) determines the steepness of the concentration versus response relationship. The value of \( E_{50} \) serves to define the opioid’s potency. Other pharmacodynamic relationships can be used when required. For example, a decreasing effect measure such as pupil constriction after opioid administration is described by

\[
E = E_0 - \frac{(E_0 - E_{\text{max}}) \cdot C_e^\gamma}{E_{50} + C_e^\gamma}
\]

If the effects are the result of agonistic action of two opioids, for example an active parent compound and its active metabolite, pupil size as a function of the opioid concentration at effect site would be described as

\[
E = E_0 - \left[ (E_0 - E_{\text{max}}) \cdot \left( \frac{C_{\text{opioid1}}}{E_{50,\text{opioid1}} + C_{\text{opioid1}}} + \frac{C_{\text{opioid2}}}{E_{50,\text{opioid2}} + C_{\text{opioid2}}} \right) \right]
\]

Other effects such as pain tolerance are better described by a linear or power model rather than a sigmoid model, because there is no ceiling of the effect:

\[
E = \text{Baseline} + a \cdot C_e^\gamma
\]

where \( a \) is the slope of the effect versus concentration relationship, and \( \gamma \) its shape factor.
This full parametric PK/PD modeling, that is, mathematical modeling of both the PK and the PD, has the disadvantage that a poor fit of the PK will carry over to the PK/PD and result in a poor PK/PD estimate. To minimize the impact of poor PK estimates on the PK/PD estimate, semi-parametric PK/PD modeling reduces the mathematical description of the PK to a minimum model consisting of linear splines, namely, of direct linear connection between subsequent concentrations. The link to the effect site compartment and the relationship between $C_e$ and the effects are similar to the full parametric PK/PD modeling.

The concepts of PK/PD modeling have direct implications for the time course of the opioid effects after various dosing regimens. Depending on the speed of the transfer between plasma and effect site, the time course of the effects can be close to the plasma concentrations or can follow them with a delay, which will be longer the slower the transfer is (Figure 2). This governs the onset and offset of the opioid effects. For an opioid with a fast transfer, that is, a large value of $k_{e0}$, the effect will start shortly after administration is started, and the effect will disappear together with the disappearance of the opioid from plasma. Thus, the effect will be controllable via the plasma concentrations. Immediate high plasma concentrations can be easily achieved with a bolus injection, and the faster the opioid disappears from plasma, the faster the effects will disappear and the patient will recover. This time course of opioid effects may be desirable, for example, in the setting of ambulatory surgery.

On the other hand, when the effects have to last longer, such as after more painful surgical procedures or for long-term analgesic treatment, an opioid such as remifentanil with rapid elimination from plasma has to be continuously administered in order to maintain the analgesic effect. Alternatively, an opioid with slower elimination from plasma can be administered. Here, a slower transfer between plasma and effect site further prolongs the clinical effects of the opioid. The slower onset with building up of sufficiently high concentrations at effect sites, possibly after several doses (Figure 2), might not be a problem for long-term therapy, or can...
be compensated by administration of a loading dose. For example, morphine has a much slower transfer rate between plasma and effect site than alfentanil or remifentanil. Therefore, it takes more time until the effect builds up but the effect lasts longer, which is an additive result of its slower elimination from the site of effect and its slower elimination from plasma as compared to remifentanil.

PK/PD Studies with Opioids

An overview about the PK/PD studies on opioids is given in Table 1. The first opioids analyzed for their PK/PD properties were fentanyl and alfentanil. Of twelve patients undergoing surgery (lumbar laminectomy, femoral-popliteal bypass, vasovasectomy, etc.), 6 received alfentanil at 1,500 µg/min and 6 received fentanyl at 150 µg/min. The EEG was continuously recorded and arterial blood samples were drawn frequently (0.5 to 1 min intervals during the infusion, and 2 to 4 min intervals thereafter, until the EEG had returned to baseline). The EEG was submitted to Fast Fourier Analysis and the 95% spectral edge was obtained as a measure of the narcotic EEG effect. The total dose required to produce delta waves was 600–825 µg for fentanyl and 6000–9000 µg for alfentanil. Onset of respiratory depression occurred after 3–5 min after starting the fentanyl infusion, and after 1–2 min after starting the alfentanil infusion. A distinct time lag was observed between peak fentanyl plasma concentration and peak changes in the spectral edge. The spectral edge changes paralleled the fentanyl concentrations, but with a temporal shift. This temporal shift was smaller with alfentanil than with fentanyl. After the end of the alfentanil infusion, the EEG returned faster to baseline than with fentanyl. A sigmoid model was used to describe the

Table 1
Parameters Estimated By Means of PK/PD Modeling of Opioids

<table>
<thead>
<tr>
<th>Opioid</th>
<th>t1/2,ke0</th>
<th>EC50 [nmol/l]</th>
<th>γ</th>
<th>Effect measure</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fentanyl</td>
<td>6.4 ± 1.3 min</td>
<td>20.5 ± 4.5</td>
<td>4.9 ± 1</td>
<td>EEG power spectrum analysis</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>6.6 ± 1.7 min</td>
<td>24.1 ± 6.5</td>
<td>6.2 ± 1.8</td>
<td>EEG power spectrum analysis (spectral edge)</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>4.7 ± 1.5 min</td>
<td>23.2 ± 7.7</td>
<td>4.3 ± 1.3</td>
<td>EEG power spectrum analysis (spectral edge)</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>5.4 ± 2.1 min</td>
<td>29.1 ± 24.7</td>
<td>4 ± 3</td>
<td>EEG power spectrum analysis (spectral edge)</td>
<td>18</td>
</tr>
<tr>
<td>Alfentanil</td>
<td>1.1 ± 0.3 min</td>
<td>1248 ± 391</td>
<td>4.8 ± 1.5</td>
<td>EEG power spectrum analysis</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>0.9 ± 0.3 min</td>
<td>1150 ± 651</td>
<td>4.8 ± 2.4</td>
<td>EEG power spectrum analysis (spectral edge)</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>0.6 ± 0.4 min</td>
<td>1385 ± 655</td>
<td>6 ± 2</td>
<td>EEG power spectrum analysis (spectral edge)</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>1 min</td>
<td>1522</td>
<td>7 ± 3.3</td>
<td>EEG power spectrum analysis (spectral edge)</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>1.3 min</td>
<td>1378</td>
<td>7 ± 3.3</td>
<td>EEG power spectrum analysis (spectral edge)</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>0.96 ± 0.81 min</td>
<td>903 ± 382</td>
<td>8.3 ± 7.5</td>
<td>EEG power spectrum analysis (spectral edge)</td>
<td>21</td>
</tr>
<tr>
<td>Sufentanil</td>
<td>6.2 ± 2.8 min</td>
<td>1.8 ± 0.8</td>
<td>3.1 ± 0.9</td>
<td>EEG power spectrum analysis (spectral edge)</td>
<td>17</td>
</tr>
<tr>
<td>Remifentanil</td>
<td>1.3 min</td>
<td>30</td>
<td>2.51</td>
<td>EEG power spectrum analysis (spectral edge)</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>1.6 ± 0.9 min</td>
<td>53 ± 14</td>
<td>4.3 ± 2</td>
<td>EEG power spectrum analysis (spectral edge)</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>1.3 ± 1.7 min</td>
<td>12 ± 9</td>
<td>1.76 ± 0.44</td>
<td>EEG power spectrum analysis (spectral edge)</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>0.79 min</td>
<td>31</td>
<td>4.27</td>
<td>EEG power spectrum analysis</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>0.8 ± 1.4 min</td>
<td>39 ± 14</td>
<td>2.8 ± 1.6</td>
<td>EEG power spectrum analysis (spectral edge)</td>
<td>22</td>
</tr>
<tr>
<td>Methadone</td>
<td>7.7 ± 3.6 min</td>
<td>1016 ± 1332</td>
<td>2.03 ± 1.1</td>
<td>Analgesia (cancer pain)</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>9 ± 14.7 min</td>
<td>1258 ± 554</td>
<td>4.4 ± 3.8</td>
<td>Analgesia (cancer pain)</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>18.6 ± 31.6 min</td>
<td>1178 ± 718</td>
<td>5.8 ± 5.4</td>
<td>Sedation</td>
<td>30</td>
</tr>
<tr>
<td>Morphine</td>
<td>2.8 h</td>
<td>34</td>
<td>1.9</td>
<td>Pupil size</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>3.9 h</td>
<td>17</td>
<td>2.1</td>
<td>Pupil size</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>2.8 h</td>
<td>27</td>
<td>2.4</td>
<td>Pupil size</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>0.6 h</td>
<td>51</td>
<td>4.27</td>
<td>EEG power spectrum analysis</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>0.9 h</td>
<td>75</td>
<td>6.4</td>
<td>EEG power spectrum analysis (spectral edge)</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>1.7 h</td>
<td>0.14</td>
<td>2.6</td>
<td>EEG power spectrum analysis (spectral edge)</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>2.6 h</td>
<td>0.208</td>
<td>2.8</td>
<td>EEG power spectrum analysis</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>0.4 h</td>
<td>0.15</td>
<td>0.6</td>
<td>EEG power spectrum analysis (spectral edge)</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>0.8 h</td>
<td>0.28</td>
<td>0.9</td>
<td>EEG power spectrum analysis (spectral edge)</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>1.2 h</td>
<td>0.28</td>
<td>2</td>
<td>EEG power spectrum analysis (spectral edge)</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>1.6 h</td>
<td>0.28</td>
<td>2.8</td>
<td>EEG power spectrum analysis (spectral edge)</td>
<td>30</td>
</tr>
<tr>
<td>M6G</td>
<td>6.4 h</td>
<td>743</td>
<td>2.6</td>
<td>Transcutaneous electrical stimuli: pain threshold</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>7.7 h</td>
<td>745</td>
<td>3.1</td>
<td>Transcutaneous electrical stimuli: pain tolerance</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>8.2 h</td>
<td>3.4</td>
<td>Transcutaneous electrical stimuli: pain tolerance</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6.2 h</td>
<td>3.4</td>
<td>Transcutaneous electrical stimuli: pain tolerance</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Piritramide</td>
<td>16.8 min</td>
<td>28</td>
<td>1.9</td>
<td>Postoperative analgesia</td>
<td>37</td>
</tr>
</tbody>
</table>

*The use of the sigmoid model here is discussed in the text.

*Only in about half of the 15 subjects could, a k.e0 parameter be proved to be part of the model. The given values are the average of the reported individual values of k.e0, with values of zero when the data were fit without a k.e0.

*A linear model was used to describe the effect versus concentration relationship; therefore, EC50 was not a parameter.
The effects of fentanyl (2.2 µg/min), alfentanil (22 µg/min), and the investigational opioid trefentanil (22 µg/min) on the EEG spectral edge were compared in five healthy volunteers in a crossover study. The estimations of the PK/PD parameters for fentanyl and alfentanil were similar to those previously obtained,15,17 trefentanil had a $b_{1/2,ke}$ of 1.2 ± 0.5 min, an $EC_{50}$ of 429 ± 313 ng/mL, and a steepness $\gamma$ of the concentration–effect relationship of 5 ± 3 for shifting the spectral edge toward lower frequencies. The maximum effects on the spectral edge were similar for all three opioids.

The PK/PD properties of alfentanil were estimated from 31 volunteers who received an intravenous bolus of 22 µg·min$^{-1}$·kg$^{-1}$ alfentanil until a plateau in the spectral edge was observed.19 The EEG was recorded and the opioid effects were quantified using the spectral edge, the delta power of the EEG and the bispectral index. The obtained PK/PD parameters were similar to those previously obtained for the EEG effects of alfentanil,15 with the exception that the $EC_{50}$ obtained with the bispectral index was significantly greater than that obtained for the increase in delta power (634 vs. 519 ng/mL); the PD parameters did not differ between the spectral edge and either delta power or bispectral index.

The PK/PD relationship for alfentanil-induced respiratory depression was investigated in a study in 14 men who underwent major urologic surgery.20 They received an intravenous infusion of 2.3 mg·min$^{-1}$·kg$^{-1}$ alfentanil until a cumulative dose of 70 µg/kg had been given, end-expiratory partial pressure of carbon dioxide exceeded 65 mmHg, or apneic periods lasting more than 60 sec occurred. The obtained PK/PD model treated CO$_2$ as an endogenous metabolite that possesses its own kinetic properties. The elimination of CO$_2$ was considered to be impeded by the opioid in a concentration-related manner. Using an indirect response model with an effect site compartment as for the EEG effects of opioids (see above), the effect of the opioid on the elimination of carbon dioxide rather than on the PaCO$_2$ itself was modeled. Because carbon dioxide is a strong respiratory stimulant, the model accounted for the fact that increasing carbon dioxide concentrations stimulate carbon dioxide elimination. The resulting PK/PD model
therefore substantially differed from the indirect-response models with sigmoid concentration-effect relationship that described well the opioid effects on the EEG. The estimated value of the $EC_{50}$ for raising the PaCO$_2$ was 60.5 µg/L. The study did not estimate the $k_{e0}$ of alfentanil.

The effects of alfentanil on the EEG spectral edge were compared with those of remifentanil in ten healthy volunteers. In a crossover design, they received intravenous infusions of 3 µg·min$^{-1}$·kg$^{-1}$ remifentanil or of 1,500 µg·min$^{-1}$ alfentanil. The study design was similar to the previous studies on EEG effects of opioids. The results for alfentanil resembled those previously obtained. Although both drugs had identical maximum effects, remifentanil was 19 times more potent than alfentanil in slowing down the EEG. Remifentanil had a transfer half-life between plasma and effect site of 1.6 min. Compared to alfentanil, the high plasma clearance of remifentanil by de-esterification via blood esterases (Figure 3), combined with its small steady-state distribution volume, resulted in a rapid decline in blood concentration after termination of an infusion. With the fast equilibration in terms of $k_{e0}$, the result of this rapid disappearance from plasma is a very quick decline of the effects of remifentanil. This decline in effects is considerably faster than with alfentanil, although the equilibration of alfentanil is at least as fast as that for remifentanil. The two PK and PK/PD properties together, that is, rapid degradation in plasma and rapid equilibration with the effect site, makes remifentanil an opioid with very fast onset and especially very fast offset of action.

The fast equilibration of remifentanil between plasma and central nervous effect site was also seen in a study in 10 healthy women who were administered an intravenous infusion at 3 mg·kg$^{-1}$·min$^{-1}$ for 10 min. Again, the EEG spectral edge was employed as an effect measure. Pharmacokinetic parameters estimated from venous and arterial data differed significantly. When arterial concentrations were plotted against electroencephalographic effect, a

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![Fig. 3. Plasma and effect site concentrations after a two-hour infusion. Although both alfentanil and remifentanil have a very fast equilibration between plasma and effect site and the effects therefore follow the plasma concentrations closely, the effects of remifentanil disappear faster than those of alfentanil. This owes to the very fast elimination of remifentanil from plasma by cleavage via blood-esterases (upper right, esteric group marked by a dotted frame), whereas alfentanil is eliminated by hepatic metabolism via CYP3A4. The dosing of the opioid has been arbitrarily adjusted to produce similar maximum concentrations.](image-url)
Classic counterclockwise hysteresis loop was observed, indicating a time lag between changes in concentration and changes in effect. However, concentrations from venous blood produced a clockwise hysteresis loop. This emphasized that with the fast degrading remifentanil, arterial blood samples need to be drawn. The study resulted in a $t_{1/2,ke}$ of 0.8 min for remifentanil, an $EC_{50}$ of 14.8 for moving the spectral edge to the left, and a shape factor $\gamma$ of the sigmoid effect versus concentration relationship of 2.8.

A further study on the EEG effects of remifentanil, with a focus on the effects of age and sex on the pharmacokinetics and the PK/PD relationship, employed a similar design and estimated similar PK/PD parameters as the previous study. Age was identified as a covariate for $EC_{50}$ and $k_{e}$. That is, the $EC_{50}$ was 13.1–0.148·(age – 40), and the $k_{e}$ was 0.595–0.007·(age – 40). This means that the $EC_{50}$ ranged from 16 ng/mL in a 20-year-old person to 7 ng/mL in an 80-year-old person; the transfer half-life for a 20-year-old person was approximately 1 min, whereas it was 2 min for an 80-year-old person. A prospective part of the study was applied to 11 participants. The median absolute prediction error of the EEG effects was 23%. Age and lean body mass were identified as covariates for various volumes and clearances of the three-compartment pharmacokinetic model that described the plasma concentration versus time course of remifentanil. Simulations of the effect site concentrations of remifentanil in populations ages 20, 50, and 80 showed that elderly patients might have occasionally a slower recovery with remifentanil than younger persons.

The PK/PD parameters of effects of remifentanil on experimental pain were investigated in 29 healthy volunteers and were compared with data obtained from 12 persons who had received alfentanil and 7 persons who had received placebo. Analgesia was evaluated by pain tolerance to pressure exerted on the tibia and on the sternum, with a maximum pressure of 10 kg/4.43 mm$^2$. A sigmoid $E_{\text{max}}$ model was used to describe the analgesic effects of the opioids. The transfer half-life between plasma and effect site was estimated to be 1.3 min, and the concentration of remifentanil producing half-maximal analgesic response (i.e., the $EC_{50}$) was estimated to be 4.66 ± 3.3 ng/mL. In addition, a steepness factor $\gamma$ of the $E_{\text{max}}$ model (equation 7) of 1.76 ± 0.44 was estimated. The use of this model may be questioned because pain tolerance did not reach a true maximum. In contrast, the maximum pressure was just an arbitrary cut-off. Therefore, a linear or power model might have been better suited to describe the rising effects of remifentanil on the painfulness of experimental stimuli. The short equilibration time found with the EEG parameters, however, was reproduced for the pain parameter.

Estimates of pain relief were assessed after a single intravenous dose (10–30 mg) of methadone to eight patients with chronic pain. The effects were related to the methadone concentrations at effect site by means of an $E_{\text{max}}$ model. No effects were observed in two patients. For the remaining 6 patients, analgesia and miosis peaked at 2–5 min after drug injection, pointing toward a short delay between plasma and site. The $t_{1/2,ke}$ ranged from 1.3 to 31.1 min, with a harmonic mean at 3.6 min. The $EC_{50}$ for pain relief with methadone was 0.29 ± 0.38 μg/mL, and the steepness $\gamma$ was 2.03 ± 1.1.

The effects of methadone were again subjected to PK/PD analysis in a study in 15 cancer patients who received continuous infusions of methadone for 180 to 270 minutes. An increase in plasma methadone concentration resulted in a rapid increase in pain relief or sedation. The values of $t_{1/2,ke}$ ranged from 3.3 to 49.5 min for pain relief, and from 2.9 to 99 min for sedation. In several patients, no $k_{e}$ was observed, that is, the delay was smaller than detectable. Pain relief was related to the concentrations at the site of effect by a sigmoid $E_{\text{max}}$ model. The model had an $EC_{50}$ of 0.359 ± 0.158 μg/mL and a steepness $\gamma$ of 4.4 ± 3.8. The parameters values for sedation were very similar.

In another study, no delay was observed between the plasma concentrations and the pupil size after oral administration of R-methadone. The parameters of the direct link sigmoid population effect model used to describe the effects of R-methadone on pupil diameter were an $EC_{50}$ of 2.3 ± 1.4 ng/mL and a shape factor $\gamma$ of 9 ± 6.2. This is 100 times less than it had been observed for pain relief. However, the sampling frequency in that study was quite slow starting at 0.5 h after methadone administration and continuing at 1, 2, 3, 4, 6 h up to 96 h. Therefore, the study might have missed the
previously observed\textsuperscript{28,29} short delay for methadone equilibration.

The analgesic effects of morphine were subjected to PK/PD modelling in a study employing transcutaneous electrical stimulation in healthy 20 volunteers.\textsuperscript{20} Morphine was administered as an intravenous bolus of 100 µg/kg followed by a one-hour infusion of 30 µg·h\textsuperscript{-1}·kg\textsuperscript{-1}. Arterial blood was sampled and the attenuation of pain threshold and pain tolerance was related to the concentrations at effect site by a sigmoid $E_{\text{max}}$ model for decreasing effect measures. The authors observed statistically significant sex differences in the PK/PD of the analgesic effects of morphine. Morphine was only half as potent in men as in women ($EC_{50}$ of 76 vs. 33 ng/mL for attenuation of pain tolerance), and it equilibrated much slower in women than in men between plasma and effect site ($t_{\frac{1}{2},\text{ke}}$ of 4.8 versus 1.6 h for women and men, respectively).

Pupil size as a measure of central nervous opioid was employed in a study in 15 healthy volunteers.\textsuperscript{31} The time course of the pupil diameter after four inhalations of each 2.2 mg morphine (1 min interval) was similar to that after 8.8 mg morphine administered intravenously. Similarity of the effects between the two morphine formulations was also observed for the respiratory depressive actions of morphine, quantified by means of carbon dioxide rebreathing.\textsuperscript{32} The effects on pupil size were related to the concentrations at effect site by a sigmoid model. The obtained values of $EC_{50}$ and $\gamma$ were 4.8 ng/mL and 2.1, respectively. Morphine equilibrated slowly between plasma and effect site, with a $t_{\frac{1}{2},\text{ke}}$ of 3.85 hours.

Recent studies employed a PK/PD modeling approach to the importance of the active metabolite of morphine, M6G, for the effects of morphine.\textsuperscript{33} Employing pupil size as a measure of central opioid effect, 8 healthy volunteers received morphine (0.5 mg as bolus, followed by 10.7 mg as infusion over 4.7 h) or M6G (10.2 mg as loading dose followed by 39.1 mg as infusion over 3.7 h) in a randomized two-way crossover study. The duration of the infusion was tailored to achieve submaximum pupil constriction, namely, a visible constriction that did not reach a plateau throughout the experiment. Pupil diameter was assessed every 20 min for approximately 18 h. The pupil size was linked to the concentrations of morphine and M6G at effect site by a sigmoid $E_{\text{max}}$ model for decreasing effects. The estimated $b_{2,\frac{1}{2},0}$ of M6G was a very slow 6.4 h, and that of morphine was 2.8 h, which resembled the previously obtained values.\textsuperscript{31} M6G was apparently 22 times less potent than morphine ($EC_{50} = 740.5$ nM for M6G vs. 36.2 nM for morphine). The steepness of the sigmoid $E_{\text{max}}$ model did not significantly differ between morphine and M6G ($\gamma$ of 1.9 and 2.6, respectively). To produce similar pupil effects, the M6G dose had to be 2.8 times greater than the morphine dose. When considering that about 10% of a morphine dose is metabolized into M6G, the metabolite apparently contributed very little to the effects of morphine.

In a subsequent study,\textsuperscript{34} the effects of morphine and M6G on pain were assessed in a placebo-controlled investigation in 12 healthy volunteers who received 63 to 112 mg of M6G or 26 to 66 mg of morphine as an intravenous bolus plus infusion for 1.8 to 6.4 h. Analgesia was assessed every 30 minutes for up to 16 hours by means of transcutaneous electrical stimulation (sine wave, 5 Hz; intensity, 0–9.99 mA). Pupil diameter and side effects were recorded concomitantly. The delay between the time course of the plasma concentrations and the time course of the effects was longer for M6G than for morphine ($t_{\frac{1}{2},\text{ke}}$ of 8.2 vs. 2.6 hours for pain tolerance, and of 7.7 hours vs. 2.8 hours for pupil diameter). The slope of the linear effect versus concentration relationship for pain tolerance was flatter for M6G than for morphine (0.05% vs. 0.6% increase in pain tolerance per nmol/L of M6G and morphine at effect site, respectively), pointing toward a lower potency of M6G as compared with morphine. M6G was also less potent than morphine in producing pupil constriction ($EC_{50}$ of 745 nmol/L vs. 26.4 nmol/L for M6G and morphine, respectively). The steepness of the concentration response relationship for the pupil data was 2.4 and 3.1 for morphine and M6G, respectively. Thus, the results of the previous study\textsuperscript{33} regarding pupil size were reproduced in that study. Again, M6G had apparently no contribution to the effects of morphine in the healthy volunteers.

The pharmacokinetic–pharmacodynamic interrelations of M6G also were addressed in a study of 10 men and 10 women who received 0.3 mg/kg intravenous M6G or placebo in a
randomized two-way crossover fashion.\textsuperscript{35} Pain tolerance to electric stimuli consisting of 10 Hz sine waves at increasing intensity (cut-off 128 mA) was used as effect measure. The delay between the time course of the plasma concentrations of M6G and the time course of the effects was long, with a transfer half-life $t_{1/2,ke0}$ of 6.2 h and a large interindividual variability of 218\% coefficient of variation. The effect site M6G concentration causing a 25\% increase in current for pain tolerance was 275 nM. For comparison, in the previous study\textsuperscript{34} that value was 500 nM for the 5 Hz electric stimuli. The shape factor of the relationship between the increase in pain tolerance and the concentrations of M6G at effect site, described by a power model (equation \textsuperscript{10}), was 0.71.

Whereas the above studies employed direct administration of M6G to assess its relative contribution to the effects of morphine, a study used a pure PK/PD modeling approach to separate the relative effects of morphine and M6G after administration of morphine only.\textsuperscript{36} After intravenous administration of 10 mg morphine sulfate to 8 healthy volunteers, thresholds to experimental heat pain evoked by means of a thermode placed at the forearm were assessed as a measure of analgesic opioid effects. The effects were related to the concentrations using a linear model. The estimated $b_{t_{1/2},ke0}$ of 0.16 h was a hybrid of morphine and M6G. It was, however, substantially shorter than previously obtained.\textsuperscript{30,31,33,34} The contribution of M6G to analgesia ranged from <0.1\% to 66\% and was inversely related to the overall effect elicited by the morphine dose. The study suggested that with increasing overall effect of morphine, the fractional contribution of M6G declines. However, because M6G administration was not employed, the results solely rely on the statistics made at the occasion of PK/PD modeling, whereas in previous studies\textsuperscript{33,34} they were supported by direct experimental evidence.

Piritramide is a $\mu$-opioid agonist that is widely used in Germany but of minor importance in other countries. In 24 patients who underwent abdominal surgery, its effects on postoperative pain were assessed. Piritramide was infused at 3 $\mu$g·min$^{-1}$·kg$^{-1}$ until analgesia was considered sufficient or up to a maximum dose of 0.2 mg/kg.\textsuperscript{37} An inhibitory sigmoid $E_{max}$ model was used to describe the relation between effect site concentration and perceived pain. The resulting $t_{1/2,ke0}$ was 16.8 min, the $EC_{50}$ was 12.1 ng/mL, and the slope factor $\gamma$ was 1.9. Because piritramide equilibrates somewhat slower than as compared to the substances of the fentanyl group, the authors advised an initial intravenous bolus of at least 5 mg when a fast onset of the analgesic effects is desired.

**Therapeutic Consequences Derived from PK/PD Modeling**

An important clinical application of PK/PD modeling is for rational opioid selection. Using published PK/PD models and parameters, the decrease in plasma fentanyl, alfentanil, and sufentanil concentration after intravenous administration by bolus injection, brief infusion, or prolonged infusion was simulated.\textsuperscript{38} These computer simulations quantified the relationship between infusion duration and the time required for recovery after termination of the infusion. The analysis suggested that alfentanil is best used for operations longer than 6–8 h, when a rapid decrease in effect site opioid concentration is desired after discontinuation of the infusion. In contrast, when fentanyl was used with infusions longer than one hour, the recovery time rapidly increased to more than 2 h (Figure 4). The time required for the effect site concentration of fentanyl and sufentanil to decrease by a given percentage increases over at least the first 10 h of the infusion, whereas it does not increase after 4 h for alfentanil. This makes alfentanil the preferable drug for infusions longer than 10 h when quick recovery of the patient is desired. Remifentanil was not yet clinically available in 1991 when these simulations were performed. Its transfer half-life between plasma and effect site, similar to that of alfentanil, together with its very fast elimination from plasma by blood esterases rather than by liver metabolism, makes it an opioid with even faster recovery than alfentanil (Figure 3).

Simulations conducted to determine the time required for a 50\% reduction in effect site concentration after an infusion designed to maintain a constant effect site concentrations similarly showed that the time required for a 50\% reduction in the effect site concentration of remifentanil was with 3.65 min. This was considerably less than that for sufentanil (33.9
Morphine has a considerably slower transfer between plasma and effect site. It appears therefore to be quite unsuitable for short-term interventions. The time to build up the effects is longer and, more importantly, the effects persist for a longer time than those of alfentanil or fentanyl. On the other hand, when longer effects are desired, morphine will require less attention to short-interval or continuous dosing, and for long-term therapy, the slower equilibration-time is no problem.

A further application of PK/PD modeling is its use for target infusion regimens. By means of computerized infusions, it is possible to maintain target opioid concentrations at effect site rather than in plasma, which provides a high degree of accuracy and controllability of the opioid therapy.

**Conclusions**

PK/PD modeling has advanced the understanding of the time course of the clinical effects of opioids after various dosing regimens. It provides a rational basis for the selection of opioids in clinical circumstances. PK/PD modeling of opioids may also be employed for the design and the interpretation of experiments addressing clinical effects of opioids.

**References**


