PHARMACOKINETICS OF THE INFUSION OF ALFENTANIL IN MAN

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SUMMARY

The pharmacokinetics of alfentanil under the conditions of an empirically derived 1-h continuous infusion of 3 \( \mu g \) kg\(^{-1}\) min\(^{-1}\), with a bolus of 80 \( \mu g \) kg\(^{-1}\), both i.v., were determined in five patients. The distribution half-life (mean±SD) (7.4±3.1 min), elimination half-life (86.7±15.8 min), apparent volume of distribution, \( V_{\text{app}} \) (0.44±0.15 litre kg\(^{-1}\)) and elimination clearance were similar to those previously reported for a single bolus of alfentanil. These values for apparent volume of distribution and clearance can be used to calculate correct bolus and infusion doses to maintain any desired steady state plasma concentration using standard formulae: for example, to maintain a steady state plasma concentration of 400 ng ml\(^{-1}\), a bolus dose of 176 \( \mu g \) kg\(^{-1}\) and an infusion of 1.3 \( \mu g \) kg\(^{-1}\) min\(^{-1}\) would be required.

Studies of the pharmacokinetics of single bolus doses of alfentanil have been reported recently (Bovill et al., 1982; Bower and Hull, 1982; Camu et al., 1982; Schuttler and Stoeckel, 1982). Compared with fentanyl, alfentanil has a smaller volume of distribution, greater binding to plasma proteins, less binding to red cells, a shorter elimination half-life, a slower total body clearance, and is less lipid soluble—characteristics which suggest that alfentanil would be an appropriate drug to give by continuous i.v. infusion.

The purpose of this study was to evaluate an i.v. bolus and infusion regimen as part of a balanced anaesthetic technique, and to determine the pharmacokinetics of alfentanil under these conditions. The bolus and infusion regimen was an empirically derived dose schedule of a bolus of 80 \( \mu g \) kg\(^{-1}\) over 30 s (\( K_{\text{bolus}} = 160 \mu g \) kg\(^{-1}\) min\(^{-1}\)) and a continuous infusion of alfentanil at a rate of 3 \( \mu g \) kg\(^{-1}\) min\(^{-1}\) (\( K_{\text{inf}} \) were started simultaneously. The infusion fluid was 60 ml of alfentanil 0.25 mg ml\(^{-1}\) solution. The infusion was given for 1 h so that each patient received a total alfentanil dose, bolus plus infusion, of 260 \( \mu g \) kg\(^{-1}\). Venous blood samples were withdrawn just before, and 2, 5, 10, 15, 30, 45 and 60 min after the start of the drug injection, and 2, 5, 10, 15, 30, 60, 120, 240 and 360 min after the infusion was discontinued. The plasma was separated and stored at \(-20^\circ\text{C}\) until assayed. Plasma concentrations were measured with a sensitive and specific radioimmunoassay (Michels, Hendricks and Heykants, 1983) by Janssen Pharmaceutica and kinetic parameters were determined by NONLIN analysis (Metzler, 1969).

Nitrous oxide was discontinued at the end of the operation which was within 10 min of the end of the infusion of alfentanil. Ventilation was assisted with oxygen until the patient was able to maintain ade-
quate spontaneous ventilation. Every 2 min the same investigator requested that the patient open his eyes. The time that this occurred was noted for later correlation with the plasma concentrations of alfentanil.

RESULTS

The patient characteristics are shown in Table I and the measured plasma concentrations for each patient in Table II. The time course of the mean plasma concentrations of alfentanil, during and after the infusion, indicate that the decay of the plasma concentrations could be described by a two-compartment model (fig. 1). Plasma concentrations decreased by 30% from their peak values over the first 10 min. Thereafter, the effect of the continuous infusion was a gradual increase in the plasma concentration until the infusion was stopped. No patient responded to painful surgical stimuli during the period of infusion or required any other anaesthetic drug(s). The plasma concentration–time curve was analysed by the NONLIN program and was divided into three parts: part one was the input of the bolus injection plus the infusion; part two was the infusion minus the elimination of the bolus, and part three was the elimination period. The equations used are presented in the appendix.

The calculated pharmacokinetic parameters are presented in Table III. The individual patient values and the mean ± standard deviation for the group are indicated.

Table I. Patient characteristics

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>Weight (kg)</th>
<th>Sex</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>34</td>
<td>84</td>
<td>M</td>
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<tr>
<td>2</td>
<td>39</td>
<td>67</td>
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<td>3</td>
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<tr>
<td>4</td>
<td>44</td>
<td>66</td>
<td>F</td>
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<tr>
<td>5</td>
<td>29</td>
<td>80</td>
<td>M</td>
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The specific response (plasma concentration–effect relationship) showed that awakening occurred when the plasma concentration decreased by a mean of 68 ± 6.4% (range 59–74%) from that measured at the time the infusion was stopped. However, there was considerable variability in the measured plasma concentrations at the time patients opened their eyes to command (178–310 ng ml⁻¹).

DISCUSSION

The alfentanil elimination half-life of the present study is in agreement with those reported recently (Bovill et al., 1982; Bower and Hull, 1982; Camu et al., 1982; Schuttler and Stoeckel, 1982). The volume of distribution (V) and elimination clearance of alfentanil in the present study are in agreement with those reported by Bower and Hull (1982), but are approximately half those reported by other workers.

The plasma concentrations of alfentanil at the times the patients responded to verbal command by opening their eyes were fairly consistent when com-

Table II. Measured plasma concentrations of alfentanil (ng ml⁻¹)

<table>
<thead>
<tr>
<th>Treatment scheme</th>
<th>Time (min)</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>Mean</th>
<th>SD</th>
<th>SEM</th>
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<tr>
<td>80-μg kg⁻¹ bolus</td>
<td>0</td>
<td>&lt;1</td>
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<td>&lt;1</td>
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<td>2</td>
<td>898</td>
<td>592</td>
<td>392</td>
<td>292</td>
<td>192</td>
<td>196</td>
<td>102</td>
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<td></td>
<td>5</td>
<td>382</td>
<td>592</td>
<td>392</td>
<td>292</td>
<td>192</td>
<td>196</td>
<td>102</td>
<td>49</td>
</tr>
<tr>
<td>3-μg kg⁻¹ min⁻¹</td>
<td>10</td>
<td>382</td>
<td>392</td>
<td>292</td>
<td>192</td>
<td>192</td>
<td>196</td>
<td>102</td>
<td>49</td>
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<tr>
<td>infusion</td>
<td>15</td>
<td>382</td>
<td>392</td>
<td>292</td>
<td>192</td>
<td>192</td>
<td>196</td>
<td>102</td>
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<td></td>
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<td>382</td>
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<tr>
<td>Infusion stopped</td>
<td>2</td>
<td>382</td>
<td>392</td>
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Contrary to observations made for fentanyl (Stoeckel, Hengstmann and Schuttler, 1979), there was no rebound increase in the plasma concentration of alfentanil during the elimination period. This suggests that recurrent postoperative ventilatory depression may not be a problem when alfentanil...
260 \mu g \text{kg}^{-1} \text{h}^{-1} \text{g} is given i.v. over 1 h.

It has been reported that a steady state plasma concentration of 400 ng ml\(^{-1}\) is necessary to provide adequate analgesia with 67% nitrous oxide (Carl C. Hug, Jr., personal communication). On the basis of the pharmacokinetic results of the present study, the correct loading dose and maintenance infusion rate to maintain a steady state plasma concentration of 400 ng ml\(^{-1}\) has been determined, using the method of Mitenko and Ogilvie (1972) to be 176 \mu g \text{kg}^{-1} \text{min}^{-1} and 1.3 \mu g \text{kg}^{-1} \text{min}^{-1}, respectively (table IV). The smaller loading dose used in the present study would account for the early decrease in the plasma concentration-time relationship and, together with the higher maintenance infusion used, for the increases in the plasma concentrations observed for the duration of the infusion; together they fortuitously maintained plasma alfentanil concentrations above the 300 ng ml\(^{-1}\) minimum recommended by Bovill and colleagues (1982). The bolus and infusion procedure recommended above should minimize variations in plasma concentrations, especially those below the therapeutic threshold, during the infusion, and result in a lower plasma concentration at the end of the infusion period and, as a result, more rapid recovery.

### APPENDIX

**DESCRIPTION OF PHARMACOKINETIC PARAMETERS**

- \(a, \beta (\text{min}^{-1})\) Slopes of distribution (\(a\)) and elimination (\(\beta\)) phases.
- \(T_a^*, T_{\beta}^* (\text{min})\) Half-lives of distribution (\(a\)) and elimination (\(\beta\)) phases, calculated from \(T_a^* = 0.693/a\) and \(T_{\beta}^* = 0.693/\beta\).
- \(\mathcal{C} (\text{ng ml}^{-1})\) Average plasma concentration during the infusion period (0–60 min), calculated from:
  \[
  \mathcal{C} = \frac{\text{AUC}_{0-60}}{60} = \frac{\text{AUC}_{0-\infty}}{60}
  \]
  where \(\text{AUC}_{0-60}\) is the area under the plasma concentration curve from 0 to 60 min (during the infusion period), as calculated by the trapezoid rule.
- \(C_{\text{le}} (\text{ml kg}^{-1} \text{min}^{-1})\) Total plasma clearance, calculated from:
  \[
  C_{\text{le}} = \frac{\text{total dose}}{\text{AUC}_{0-\infty}} = (80 + 180) \mu g \text{kg}^{-1} / \text{AUC}_{0-\infty}
  \]
- \(V_{\text{are}} (\text{litre kg}^{-1})\) Apparent volume of distribution calculated from:
  \[
  V_{\text{are}} = C_{\text{le}} \times \frac{1}{k_a}
  \]
- \(V_{\text{are}} (\text{litre})\) Apparent volume of distribution taking into account the body weight (kg) of the patient.
- \(k_{h1}, k_{h2} (\text{h}^{-1})\) Rate constants between the central compartment (\(C_1\)) and the peripheral compartment (\(C_2\)).
- \(k_{h10} (\text{h}^{-1})\) Rate constant for elimination from the central compartment.
- \(V_{1}, V_2 (\text{litre kg}^{-1})\) Volume of the central compartment (\(V_1\)) and volume of the peripheral compartment (\(V_2\)) taking into account the body weight (kg) of the patient. \(k_{h1}, k_{h2}, k_{h10}, V_1\) and \(V_2\) were calculated from:
  - **Bolus + infusion (0–30 s)**
    \[
    \frac{dC_1}{dt} = (k_{\text{bolus}} + k_{\text{inf}}) \frac{V_1}{k_{h10}} + k_{h10} \frac{V_2}{k_{h10}} - (k_{h2} + k_{h10}) \frac{C_1}{k_{h10}}
    \]
  - **Infusion (30 s to 1 h)**
    \[
    \frac{dC_1}{dt} = k_{\text{inf}} \frac{V_1}{k_{h10}} + k_{h10} \frac{V_2}{k_{h10}} - (k_{h2} + k_{h10}) \frac{C_1}{k_{h10}}
    \]
    \[
    \frac{dC_2}{dt} = \text{same as bolus + infusion (0–30 s)}
    \]
  - **Elimination (1 h to infinity)**
    \[
    \frac{dC_1}{dt} = k_{h10} \frac{V_1}{k_{h10}} + k_{h10} \frac{V_2}{k_{h10}} - (k_{h2} + k_{h10}) \frac{C_1}{k_{h10}}
    \]
    \[
    \frac{dC_2}{dt} = \text{same as bolus + infusion (0–30 s)}
    \]

### ACKNOWLEDGEMENTS

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### REFERENCES


PHARMACOCINETIQUE D'UNE PERFUSION D'ALFENTANIL CHEZ L'HOMME

RESUME
Nous avons étudié la pharmacocinétique de l'alfentanil administré en perfusion intraveineuse continue d’une heure, ajustée empiriquement à la dose de 3 μg kg⁻¹ min⁻¹ après un bolus de 80 μg kg⁻¹ chez cinq patients. La demi-vie de distribution (moyenne ± DS) (7,4 ± 3,1 min), la demi-vie d’élimination (86,7 ± 15,8 min), le volume apparent de distribution, Vₚₑₑₚₑₑ (0,44 ± 0,15 litre kg⁻¹) et la clairance d’élimination (3,33 ± 0,75 ml kg⁻¹ min⁻¹) étaient semblables à ceux précédemment retrouvés pour une injection flash unique d’alfentanil. Ces valeurs de clairance et de volume apparent de distribution peuvent être utilisées pour calculer les doses de charge et d’entretien qui permettent de maintenir, de façon stable, une concentration plasmatique souhaitée quelle qu’elle soit, en utilisant les formules usuelles: par exemple, pour maintenir une concentration plasmatique stable de 400 ng ml⁻¹, il faudra une dose de charge de 176 μg kg⁻¹ et une perfusion d’entretien de 1,3 μg kg⁻¹ min⁻¹.

FARMACOCINETICA DE LA INFUSION DE ALFENTANILO EN EL HOMBRE

SUMARIO
En cinco pacientes, determinó la farmacocinética del alfentanilo bajo las condiciones de una infusión continua de 1 h derivada empíricamente de 3 μg kg⁻¹ min⁻¹, con un bolo de 80 μg kg⁻¹, ambas i.v. La media vida de distribución (promedio ± SD) (7,4 ± 3,1 min) la media vida de eliminación (86,7 ± 15,8 min), el volumen aparente de distribución, Vₚₑₑₚₑₑ (0,44 ± 0,15 litre kg⁻¹) y la evacuación (3,33 ± 0,75 ml kg⁻¹ min⁻¹) eran similares a los previamente indicados con un bolo único de alfentanilo. Esos valores del volumen aparente de distribución y de evacuación pueden usarse para calcular el bolo correcto y las dosis de infusión necesarias para mantener cualquier concentración deseada en estado estable en el plasma al usar fórmulas normales: por ejemplo, para mantener una concentración en estado estable en el plasma de 400 ng ml⁻¹, se necesitarían una dosis de bolo de 176 μg kg⁻¹ y una infusión de 1,3 μg kg⁻¹ min⁻¹.

PHARMAKOKINETIK VON ALFENTANILINFUSIONEN BEIM MENSCHEN

ZUSAMMENFASSUNG
Bei fünf Patienten wurde die Pharmakokinetik von Alfentanil während einer empirisch abgeleiteten einstündigen kontinuierlichen Infusion von 3 μg kg⁻¹ min⁻¹ nach einem Bolus von 80 μg kg⁻¹, beides i.v. gegeben, bestimmt. Die Verteilungshalbwertzeit (mean±SD) (7,4 ± 3,1 min), Eliminations-Halbwertzeit (86,7 ± 15,8 min), Verteilungsvolumen (Vₚₑₑₚₑₑ) (0,44 ± 0,15 litre kg⁻¹) und Eliminations-Clearance (3,33 ± 0,75 ml kg⁻¹ min⁻¹) entsprachen den früher berichteten Werten nach einem Einzelbolus. Die Werte für Verteilungsvolumen und Clearance können zur Errechnung notwendiger Bolus- und Infusionsdosen zur Aufrechterhaltung jeder gewünschten Steady-state-Plasmakonzentrationen dienen. Um beispielsweise eine Plasmakonzentration von 400 ng ml⁻¹ aufrechtzuerhalten, sind eine Bolusinjektion von 176 μg kg⁻¹ und eine Infusion von 1,3 μg kg⁻¹ min⁻¹ notwendig.