PULMONARY KINETICS OF FENTANYL AND ALFENTANIL IN SURGICAL PATIENTS

K. TAEGER, E. WENINGER, F. SCHMELZER, M. ADT, N. FRANKE AND K. PETER

Lipid-soluble basic drugs may be sequestered as the drug-loaded blood passes through the pulmonary capillaries [1], and the amount of drug remaining in the blood for distribution to the organism may be substantially reduced by this mechanism. The temporary sequestration of a significant proportion of an i.v. dose of a drug by the lung may influence the intensity and duration of its pharmacological effect [2].

Hess, Herz and Friedel [3] reported that rabbit lung had a high affinity for fentanyl: approximately 24% of the dose administered was sequestered as the drug passed through the lung for the first time (“first pass”). Several reports demonstrated a high fentanyl binding capacity of the human lung [4–7].

This paper describes quantitatively the pulmonary kinetics of fentanyl and alfentanil in patients suffering from coronary artery disease.

PATIENTS AND METHODS

After approval was granted by the local ethics committee for an investigation into the pulmonary kinetics of fentanyl and alfentanil in surgical patients, informed consent was obtained from 11 patients (10 male) scheduled to undergo elective coronary artery bypass surgery. Patients ranged in age from 36 to 67 yr and in body weight from 71 to 81 kg. They were divided into two groups: fentanyl (five patients; Nos 1–5. No. 5 was the female patient); and alfentanil (six patients; Nos I–VI). Patient I was the only one with any impairment of lung, liver, or kidney function—he...
suffered from nephrotic syndrome as a result of a mesangioproliferative glomerulonephritis.

About 60 min before the induction of anaesthesia, all patients received flunitrazepam 1 mg i.m. and morphine sulphate 10 mg s.c. Anaesthesia was induced with flunitrazepam 0.5–1.0 mg and etomidate 18–20 mg. Pancuronium 0.1 mg/kg body weight was used to provide neuromuscular blockade. Anaesthesia was maintained with nitrous oxide in oxygen (1:1) and 0.2–1.0 vol% enflurane. Ventilation was controlled mechanically. Central venous and pulmonary artery catheters were inserted and their correct positioning verified by radiography. A three-way stopcock was connected to the arterial cannula (Abbocath 16 gauge, femoral artery) via a 15-cm piece of connecting tubing. A freshly prepared mixture of approximately 10 mg of indocyanine green (Cardiogreen, Paesel, Frankfurt, FRG) and fentanyl base 0.3 mg or alfentanil base 8 mg was administered as a single injection through the central venous catheter. The exact amounts of dye and opioid administered were measured by weighing the syringes before and after filling and taking into account the deadspace of syringe, three-way stopcock and central venous catheter. Immediately after the end of the injection, samples of arterial blood were collected at 1-s intervals by directing the spontaneous outflow of the arterial catheter into 48 labelled, heparinized plastic tubes. From 25 to 35 s and 35 to 45 s after the injection, two samples of mixed venous blood were collected. Further arterial and mixed venous blood samples were drawn simultaneously 1, 2, 3, 4, 5, 6, 8, 10, 12 and 14 min after injection. Each dye solution was calibrated separately. Calibration curves were constructed using blank plasma from each patient. After appropriate dilution, the indocyanine green concentration in the plasma samples was determined spectrophotometrically at 805 nm.

Fentanyl blood and plasma concentrations greater than 5–10 ng ml\(^{-1}\) were measured by gas chromatography (Hewlett Packard 5840 A, PND-detector) as described by Gillespie and co-workers [8]. Alfentanil was used as the internal standard. Because of the limited sensitivity of the gas chromatographic method, fentanyl blood concentrations of less than 5 ng ml\(^{-1}\) were derived from measurements of the plasma concentrations, determined by radioimmunoassay (FEN-RIA 200, Institut National des Radioelements, Fleurus, Belgium) and the blood:plasma concentration ratios. Alfentanil concentrations were measured by gas chromatography with R 38527 as the internal standard (a gift of Janssen Pharmaceutics, Beerse, Belgium). Table I summarizes the coefficients of variation of the three methods, calculated from measurements of standards of different concentrations.

**Calculations**

Extrapolation of the downslope of the dye dilution curves and calculations of mean transit time, cardiac output and central blood volume were performed with the aid of a program for a hand-held computer, published by Lin [9].

The opioid content of the lung at mean transit time was calculated from the difference between the net amount of the opioid injected and the amount of opioid which appeared on the arterial side until mean transit time. The “missing” amount of drug is the pulmonary opioid content at mean transit time. The release of alfentanil from the lung was estimated from the area between the arterial and mixed venous blood concentrations and cardiac output which was assumed to be unchanged for 2–3 min after injection. In the case of fentanyl, the decreasing pulmonary opioid content with time was calculated from the area between the arterial and mixed venous blood concentrations, using non-linear least squares regression analysis of the arterial–
mixed venous concentration differences. (For further details see Appendix.)

**RESULTS**

The changes in the concentrations of indocyanine green in arterial plasma, and of fentanyl in arterial blood, a few seconds after the administration of fentanyl base 0.263 mg and 9.6 mg of the dye to patient No. 5 are shown in figure 1. Over the whole of the period of observation the concentration of fentanyl in arterial blood was greater than that in mixed venous blood. The patient had a cardiac output of 4921 ml min\(^{-1}\) and a central blood volume of 1215 ml. Mean fentanyl blood concentration (63.1 ng ml\(^{-1}\)) during first pass of the bolus multiplied by central blood volume equals the amount which passed the lungs (76667 ng). Therefore, the lungs sequestered approximately 71% of the dose during this first
Table III. Fentanyl concentrations (ng ml⁻¹) in arterial (a) and mixed venous (v) blood

<table>
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<tr>
<th>Time (min)</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
<th>Patient 5</th>
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<tr>
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<td>36.0</td>
<td>24.7</td>
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<tr>
<td>0.66</td>
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<td>24.5</td>
<td>19.8</td>
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<td>28.7</td>
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<td>18.4</td>
<td>10.0</td>
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<td>14.0</td>
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<tr>
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<td>9.2</td>
<td>17.0</td>
<td>16.3</td>
</tr>
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<td>3</td>
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<td>12.6</td>
<td>7.6</td>
<td>13.6</td>
<td>13.5</td>
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<tr>
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<td>5.2</td>
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</tr>
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<td>14</td>
<td>5.0</td>
<td>4.4</td>
<td>4.5</td>
<td>3.6</td>
<td>6.4</td>
</tr>
</tbody>
</table>

FIG. 2. Time course of the arterial–mixed venous concentration differences of fentanyl (Cₐ₋ₐᵥ) in arterial blood of patients Nos 1–5. Calculated regression lines are depicted.
pass of the fentanyl-loaded blood through the pulmonary circulation. The respective figures for patients Nos 1–4 are listed in table II. Corresponding fentanyl concentrations in arterial and mixed venous blood are summarized in table III. In any case, and for the whole of the period of observation, the concentrations in arterial blood exceeded those in mixed venous blood. In figure 2 the time courses of the arterial–mixed venous concentration differences and the regression lines are depicted for patients Nos 1–5. According to the results of the regression analysis, all profiles were best described by two-term, exponential equations. Coefficients and exponents are listed in table IV.

The complete quantitative determination of the pulmonary kinetics of fentanyl during the 14 min following injection is shown in figure 3. Of the 43.0–86.9% of the dose which accumulated during first pass of the fentanyl bolus through the pulmonary vascular bed, a considerable part was released during the first 2 min. Thereafter, evenly decreasing amounts of the opioid were washed out. At the end of the observation period, pulmonary fentanyl content was less than 20% of the dose in four patients. Only in patient No. 2, whose lungs had the highest fentanyl affinity, was more than 40% of the dose stored by pulmonary tissues at that time.

Half times of the pulmonary clearance of fentanyl were calculated from the data in table IV: median $T_{\text{fast}}$ 0.22 min (range 0.16–0.27); median $T_{\text{slow}}$ 5.78 min (range 3.65–13.86).

Figure 4 demonstrates the changes in alfentanil concentration in arterial and mixed venous blood, and of indocyanine green in arterial plasma after the bolus administration of alfentanil base 7.27 mg and 9.76 mg of the dye to patient No. III. As in the case of fentanyl (fig. 1), the opioid reached its maximum concentration shortly after the dye. Between 1 and 2 min after injection, the arterial–mixed venous alfentanil concentration difference approached zero. The same was true for the remaining five patients who received alfentanil. In the case of patient III, we calculated a cardiac output of 5462 ml min$^{-1}$ and a central blood volume of 1334 ml. During first pass of the opioid through the pulmonary circulation, 53.7% of the administered dose was taken up by the lungs.

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**Table IV. Coefficients and exponents of two-term exponential equations which describe the time course of the arterial–mixed venous blood concentration differences of fentanyl**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>A</th>
<th>$\alpha$</th>
<th>B</th>
<th>$\beta$</th>
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<td>39.4</td>
<td>3.18</td>
<td>3.4</td>
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</tr>
<tr>
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<td>79.1</td>
<td>3.50</td>
<td>3.5</td>
<td>0.16</td>
</tr>
<tr>
<td>4</td>
<td>36.6</td>
<td>2.55</td>
<td>4.9</td>
<td>0.12</td>
</tr>
<tr>
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<td>23.5</td>
<td>2.94</td>
<td>4.8</td>
<td>0.10</td>
</tr>
</tbody>
</table>

Fig. 3. Results of the study of pulmonary kinetics in five patients. The ordinate gives the amount of drug sequestered by the lung in relation to the dose applied.
The corresponding figures for patients Nos I–VI are listed in table V. Between 35.9 and 79.8% of the injected amount was sequestered during the first pass of the alfentanil bolus through the lungs. Only 20.2–64.1% of the dose was available for further distribution to the organism at that time. The pulmonary alfentanil content for the first 2–3 min after injection is shown in figure 5. While, in four patients, the pulmonary alfentanil content decreased rapidly to less than 20% and, in the case of patient No. VI, approached zero, the lungs of two patients still stored almost 50% of the dose 2 min after administration. The median of the half-times of the rapid alfentanil release was 0.28 min (range 0.08–0.51 min).

### DISCUSSION

The lungs are engaged in a variety of non-respiratory functions. Because of their strategic position in the systemic circulation and their unique anatomical construction, they may make a considerable contribution to the metabolism and accumulation of many endogenous and exogenous compounds [10–12]. The local anaesthetic agents bupivacaine, mepivacaine and lignocaine have

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**FIG. 4.** Time course of concentrations of the dye in arterial plasma (●) and of alfentanil in arterial (▲) and mixed venous (○) blood of patient III. Note the early disappearance of the arterial–mixed venous blood concentration difference.

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**TABLE V.** Alfentanil dose, haemodynamic variables and pulmonary alfentanil content at mean transit time. \( D = \) net amount of alfentanil injected; \( t_m = \) mean transit time; \( CO = \) cardiac output; \( CBV = \) central blood volume; \( \bar{C}_O = \) mean of the alfentanil blood concentrations during first pass; \( C_A = \) alfentanil content of the lung after first pass relative to \( D \)

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>( D (\mu g) )</th>
<th>( t_m ) (s)</th>
<th>( CO ) (ml min(^{-1}))</th>
<th>( CBV ) (ml)</th>
<th>( \bar{C}_O ) (( \mu g ) ml(^{-1}))</th>
<th>( C_A ) (%)</th>
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<td>3091</td>
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<td>2.24</td>
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</tr>
<tr>
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been shown to accumulate in pulmonary tissue, as do propranolol, morphine, methadone, amphetamine and many other drugs [13]. Any drug injected i.v. for therapeutic purposes must pass the pulmonary vascular bed in a quantity sufficient to exert its pharmacological effects on its target [2]. Substantial pulmonary uptake of a drug may decrease its toxicity by reducing the peak blood concentration, or it may result in a slow release of the drug into the systemic circulation, thereby preventing it from being biotransformed or stored in peripheral tissues, and prolonging its effects. Among xenobiotics, lipid soluble basic amines seem to be most susceptible to sequestration by the lung. Even highly lipophilic neutral or anionic drugs do not accumulate to a significant degree within the lung [1, 2, 14].

Hess and colleagues [3] published the results of their investigation on the time course of the distribution of fentanyl in rabbits. Thirty seconds after the injection of $^{14}$C-fentanyl, 24% of the injected dose was retained in the lung. Thereafter, the substance diffused back from the lung into the blood. At any time studied, the fentanyl content of the pulmonary tissue exceeded by far the concentration in any other tissue, including fat. Five minutes after injection, the lung tissue still had a concentration about 100 times greater than that in plasma. Five to 10 min after injection, the depot function of the lung was no longer important. The results of that study were confirmed by Rigg and co-workers [15]. In rats, the pulmonary sequestration of fentanyl was found to be far less [16]. During cardiopulmonary bypass, Bentley [4] observed considerable pulmonary accumulation of fentanyl in patients. After restoration of perfusion and resumption of artificial ventilation, the stored fentanyl was released into the blood stream. Pulmonary sequestration of fentanyl in patients has also been observed by Cartwright and associates [5] and Koska and colleagues [6]. However, there was no quantitative description of pulmonary kinetics of this opioid in man. The results of our investigation, based on the simultaneous determination of haemodynamic variables and opioid concentrations in arterial and mixed venous blood, demonstrate the accumulation of a considerable proportion of the amount injected on the first pass of the fentanyl through the lung. Between 43.0 and 86.9% (median 70.9%) of the fentanyl dose left the blood stream, being sequestered by pulmonary tissue. Recently, Roerig and co-workers [7] confirmed our results [17] with respect to the first-pass uptake of fentanyl. They found that 63–87% (75.2 (3.2))% of a single dose of fentanyl was taken up by the lung in surgical patients who showed no evidence of lung disease. The washout of fentanyl from the lung, initially proceeding rapidly and then more slowly, points to the existence of two distinct binding sites with different binding forces. In the case of patient No. 2, whose lung had the highest affinity for fentanyl, 14 min after injection, 40% of the amount administered was still stored by the lung.

Alfentanil was sequestered to a similar extent when the alfentanil-loaded blood first passed the pulmonary circulation. During mean transit time, 20.2–64.1% of the amount injected was found in arterial blood. Therefore, 35.9–79.8% (median 58.6%) was stored in the lung. The subsequent release was initially of a similar magnitude, when compared with fentanyl, as can be seen from the medians of the half-times describing the fast release: fentanyl $T_{1/2} = 0.22$ (0.16–0.27) min; alfentanil $T_{1/2} = 0.28$ (0.08–0.51) min.

One to three minutes after injection, the arterial–mixed venous alfentanil concentration difference disappeared; that is, there was no longer a detectable release of opioid, although in five of six patients between 15% and nearly 50% of the
administered dose was still sequestered by the lung. The early disappearance of the concentration difference between simultaneously drawn blood samples from the femoral and the pulmonary artery agrees with the results of De Lange and colleagues [18], who studied pulmonary alfentanil kinetics, beginning 5 min after i.v. injection. They could not detect any concentration difference. The initial rapid release of alfentanil from the lung and the probably long-lasting storage function of the lung for a considerable part of the injected alfentanil, at least in some patients, points again to the existence of two binding sites—one of which might be shared with fentanyl. The other site, apparently, has such a high binding energy as to make detection of the alfentanil release impossible. Its release is further obscured by the fact that the lung receives the whole cardiac output. Two distinct binding sites within the pulmonary tissues have been established for lignocaine [19] and methadone [20].

Fentanyl and alfentanil both are lipid soluble drugs, alfentanil less so than fentanyl [21]. However, the pulmonary capillary endothelium, constructed to allow for rapid exchange, will not delay the distribution of alfentanil within pulmonary tissues, since its diffusion is not even impeded across the blood–brain barrier [21]. At pH 7.4, 91% of fentanyl ($pK_a = 8.43$) and 11% of alfentanil ($pK_a = 6.5$) exist in the cationic form [21]. These drugs are mainly bound by hydrophobic interaction [22]. Whether, and to what extent, the cationic form is bound to the negatively charged groups of phospholipids [14] remains to be elucidated. The anatomical location of the binding sites is uncertain, but it may, to some degree, consist of alveolar surfactant. The lipid-soluble opioids might associate with phospholipids of the pulmonary extracellular lining layer, the phospholipid rich lamellar bodies of the type II-cells or the phospholipids of pulmonary endothelium [1, 2, 23]. Jorfeldt and associates [24], studying the pulmonary kinetics of lignocaine, could not detect any marked influence of severe lung impairment on the pulmonary uptake of lignocaine. However, the pulmonary surfactant content of patients suffering from adult respiratory distress syndrome does not differ quantitatively from individuals with an intact lung [25]. General anaesthesia, or the presence in the circulation of another local anaesthetic agent, mepivacaine, in pharmacologically active concentrations did not influence lignocaine uptake either. Lignocaine first-pass uptake by human lung (34–84% of the amount injected [24]) has been shown to be independent of energy and not carrier mediated [26]. Therefore, lignocaine and probably most other substances are taken up by passive diffusion. Changes of the acid–base equilibrium strongly influenced lignocaine uptake [26]. The uptake of lignocaine is higher at an alkaline than at a neutral pH. A similar pH-dependence of the accumulation of fentanyl in brain tissue (in dogs) has been reported by Ainslie [27]. Therefore, pH differences might be one of the otherwise unknown reasons for the high interindividual variability of the pulmonary accumulation of both opioids.

Jorfeldt [24] reported another interesting observation. In patients receiving mepivacaine by infusion, the arterial concentration of mepivacaine increased temporarily after the bolus injection of lignocaine. This probably reflects a displacement of the local anaesthetic from binding sites shared by both drugs. On the other hand, an infusion of mepivacaine had no measurable influence on pulmonary lignocaine sequestration. Pulmonary tissues might be a source of secondary increases of serum fentanyl or alfentanil concentrations that have been reported by a number of investigators. Should the opioids be released from muscle or intestines into venous blood, pulmonary sequestration will reduce the secondary increase in the blood concentration on the arterial side considerably.

The accumulation of endogenous and exogenous substances by the lung may be limited as a result of a finite number of non-specific binding sites. Capacity-limited binding has been found in the case of noradrenaline [10] and propranolol [28], the pulmonary uptake of which was dramatically reduced in patients who were receiving propranolol treatment regularly. On the other hand, the sequestration of morphine was independent of the amount injected over a wide range of doses [29]. Whether or not the pulmonary accumulation of fentanyl or alfentanil depends on their concentration is unknown.

The existence of a variety of xenobiotic-metabolizing enzymes in the lung has been clearly established [10, 23]. In vitro studies indicate a spectrum of enzyme activities almost as wide as that found in the liver [23]. The time course of the release of fentanyl and alfentanil in our patients (figs 3 and 5) is not indicative of a substantial contribution of the lung to overall elimination of
these opioids. In the case of fentanyl, extrapolation of the downslope of the clearance curve (fig. 3) seems to approach zero; that is all the sequestered fentanyl is finally washed out unchanged. In the case of alfentanil, the complete disappearance of an arterial–mixed venous concentration difference very soon after injection more or less excludes a relevant biotransformation of the drug by human pulmonary tissue.

Both opioids are sequestered by pulmonary tissues in amounts sufficient to reduce substantially that remaining in the blood for distribution to the brain and other organs. This mechanism delays their transport to the sites of action, prolongs—at least in case of fentanyl—the time necessary to reach the maximum clinical effect, and reduces the intensity of these effects. The continuous release of fentanyl may prolong the duration of its clinical effects. In the case of alfentanil, the strong binding of a considerable part of the dose might influence its elimination half-life by contributing to low blood concentrations and preventing the drug from being biotransformed faster. The high interindividual variability of the pulmonary accumulation of these opioids presumably is of some influence on the dose necessary to release surgical pain.

APPENDIX

ABBREVIATIONS USED

- $A_v, A_A$: pulmonary opioid content of fentanyl or alfentanil at mean transit time
- $D$: net amount of opioid injected i.v.
- $CBV$: central blood volume
- $t_m$: mean transit time
- $C_0$: average of opioid concentrations of arterial blood between time of injection and $t_m$
- $AUC$: area between arterial and mixed venous opioid concentrations in blood
- $AUC_{tm \to \infty}$: AUC from $t_m$ to infinity
- $AUC_{t \to \infty}$: AUC from time $t$ to infinity
- $(C_{A_{ten}} - C_{V_{ten}})$: arterial–mixed venous fentanyl concentration difference
- $A, B, \alpha, \beta$: coefficients and exponents of two-term exponential equations, describing the time course of the drug concentration differences of arterial and mixed venous blood
- $FCO_{tm \to t_x}$: fraction of cardiac output from $t_m$ to $t_x$

CALCULATIONS

1. Pulmonary opioid content at mean transit time:
   
   $$A_v, A_A = D - CBV \cdot C_0$$

2. Pulmonary fentanyl content at time $t$ ($A_{f,t}$):
   
   Non-linear least squares regression analysis of the differences of the corresponding concentrations of arterial and mixed venous blood (Hewlett-Packard 9845 A, software “Nonlinear regression analysis”), yielding optimized values for $A, B, \alpha, \beta$.

   If fentanyl is not being biotransformed by pulmonary tissue, then

   $$A_v = A_{f, \text{released}} = \text{const} \times \frac{\text{AUC}_{tm \to \infty}}{\text{AUC}_{t \to \infty}}$$

   The pulmonary fentanyl content as a function of time ($A_{f,t}$) can be expressed in terms of fractional area [30–33]:

   $$A_{f,t} = A_v \cdot \frac{\text{AUC}_{tm \to \infty}}{\text{AUC}_{t \to \infty}}$$

   If the time course of the arterial–mixed venous blood concentration difference can be described by the well known two-term exponential equation:

   $$(C_{A_{ten}} - C_{V_{ten}}) = A \cdot e^{-\alpha t} + B \cdot e^{-\beta t}$$

   then:

   $$\text{AUC}_{tm \to \infty} = \frac{A}{\alpha} + \frac{B}{\beta}$$

   and

   $$A_{f,t} = A_v \cdot \frac{A \cdot e^{-\alpha t} + B \cdot e^{-\beta t}}{\frac{A}{\alpha} + \frac{B}{\beta}}$$

   $A_{f,t}$ expressed as part of $D$:

   $$A_{f,t} = \frac{A \cdot e^{-\alpha t} + B \cdot e^{-\beta t}}{\frac{A}{\alpha} + \frac{B}{\beta}} \cdot \frac{100}{D}$$

3. Pulmonary alfentanil content from $t_m$ to the moment of the disappearance of the arterial–mixed venous concentration difference ($t_x$; it is assumed that cardiac output did not change for about 2–3 min after injection):

   $$A_{f,t} = A_A \cdot FC_{0,tm \to t_x}$$

4. Calculation of half times:

   $$T_{1/2}^{A_f} = 0.693 / \alpha, \beta.$$

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