Infusion system for hydromorphone

Hydromorphone was administered using an infusion pump (Braun Perfusor FM®, B. Braun, Melsungen, Germany), which was controlled by a laptop computer running the control software ivFeedPCA 1.1 (H. Ihmsen and C. Jeleazcov, Department of Anesthesiology, University Hospital Erlangen, Germany). This software, written in Visual Basic 6.0, is a further development of the software ivFeed (H. Ihmsen and H. Schwilden, Department of Anaesthesiology, University Hospital Erlangen, Germany) which was developed for closed-loop feedback control of intravenous drugs.[1]

The infusion rate necessary to achieve and maintain a defined plasma concentration is calculated based on the pharmacokinetic model of the drug by applying the principles of linear pharmacokinetics for multicompartment models.[2] Given the disposition function G(t) of the drug, the concentration c(t) for any infusion scheme I(t) can be calculated by the convolution integral

$$c(t) = \int_0^t G(t-\tau) \cdot I(\tau) \cdot d\tau \quad (1)$$

where the disposition function G(t) is just the concentration time course c(t) after a bolus of unit dose. For a multicompartment model with m compartments the disposition function is a sum of m exponential terms:

$$G(t) = \sum_{i=1}^{m} A_i \cdot e^{-\lambda_i t} \quad (2)$$

where the coefficients A_i and exponents λ_i can be calculated from the clearances Cl_i and the volumes of distribution V_i.

In technical realizations,[3] the continuous variables c(t), G(t) and I(t) are calculated at discrete time points t_1, t_2, t_3, ... with $t_{n+1}=t_n+\Delta t$. In the software ivFeedPCA we use a $\Delta t=10$ sec. Further on, the infusion rate within the interval $[t_n, t_{n+1}]$ is constant and has the value I_n. Solving the equations (1) and (2) leads then to the following recursive formulas:

$$c(t_n) = \sum_{i=1}^{m} A_i \cdot r_i(t_n) \qquad (3)$$

$$r_i(t_{n+1}) = r_i(t_n) \cdot e^{-\lambda_i \Delta t} + \frac{I_n}{\lambda_i} \cdot (1 - e^{-\lambda_i \Delta t}) \qquad (4)$$

The time series usually starts at t=0 with $r_i(0)=0$, and the equations (3) and (4) are then updated in steps of Δt.

In case of target controlled infusion (TCI), one has the concentration $c(t_n)$ at time t_n (which means that one knows also the corresponding $r_i(t_n)$) and wants to reach a target concentration c_{Target} at time t_{n+1}, i.e. $c(t_{n+1})=c_{Target}$. Equations (3) and (4) can then be used to determine the necessary infusion rate I_n to be administered within the next time interval $[t_n,t_{n+1}]$:

$$I_n = \frac{c_{Target} - S_1(t_n)}{S_2} \qquad (5)$$

$$S_1(t_n) = \sum_{i=1}^{m} r_i(t_n) \cdot A_i \cdot e^{-\lambda_i \Delta t} \qquad (6)$$

$$S_2 = \sum_{i=1}^{m} \frac{A_i}{\lambda_i} \cdot (1 - e^{-\lambda_i \Delta t}) \qquad (7)$$

The following constraints must be observed: if $I_n<0$ then $I_n=0$ (this happens if $c_{Target}<c(t_n)$), and if $I_n>I_{max}$ then $I_n=I_{max}$, where I_{max} is the maximum allowed infusion rate.

When the software ivFeedPCA is used in TCI mode, the anesthetist sets the target concentration c_{Target} via the graphical interface of the software. In TCI-patient controlled analgesia (PCA) mode, the patient can change the target. To facilitate this, a push-button was connected via a serial port to the laptop. When the button is pressed, a target increase request message appears on the graphical interface, and after the anesthetist has confirmed this request, the target is increased in a predefined step. (The confirmation of the target increase request is a safety function in the experimental system setup used in this study. In future versions, the system may automatically increase the target on request, similar to the bolus dose on request in standard PCA). In order to avoid overdosing, no further target increase is possible within a predefined lock-out time. Without any requests the target is reduced automatically in predefined steps until a predefined minimum target concentration is reached. At any time, the anesthetist can switch between TCI and TCI-PCA mode.

Based on the drug concentration in the syringe, the calculated infusion rate (given in mg/min) is converted into a delivery rate (in ml/h) and this delivery rate is transmitted to the infusion pump via a serial port. The actual delivery rate of the pump is also transmitted back to the computer so that discontinuation of the drug delivery (e.g. during change of the syringe) will be detected and compensated by an additional dose as soon as the drug delivery is continued.

The software ivFeedPCA contains in its database the pharmacokinetic parameters of numerous intravenous drugs (as e.g. propofol, ketamine, midazolam, alfentanil, sufentanil, remifentanil, hydromorphone) together with additional information as e.g. maximum infusion rate, drug concentration in the syringe, etc. All actions as e.g. change of the control mode or change of the target concentration as well as the infusion rates and the calculated concentrations at each time are stored in protocol files.

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2. Schwilden H: A general method for calculating the dosage scheme in linear pharmacokinetics. Eur J Clin Pharmacol 1981; 20: 379-86
3. Bailey MJ, Shafer SL: A Simple Analytical Solution to the Three-Compartment Pharmacokinetic Model Suitable for Computer-Controlled Infusion Pumps. IEEE Trans Biomed Eng 1991; 38: 522-5