Context-sensitive half-time of fentanyl in dogs

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ABSTRACT. Context-sensitive half-times (CSHTs) of fentanyl in dogs were determined using pharmacokinetic models reported by Murphy et al. and Sano et al., and compared with a human model. The CSHT was defined as the time required for a 50% decrease in drug concentration in the central compartment after the termination of infusion. Although CSHTs increased gradually as the infusion time increased, the CSHTs in dogs were shorter than those in humans. The CSHTs at steady-state were 31.3 and 69.2 min in dogs, and 306.5 min in humans. The CSHTs of fentanyl in dogs are apparently shorter than those in humans; therefore, a continuous infusion of fentanyl may be a rational regimen in dogs, even if duration of infusion is extended.

KEY WORDS: canine, fentanyl, half-time, infusion, pharmacokinetics

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Fentanyl is one of the most widely used perioperative analgesics in dogs [3, 4, 6]. Fentanyl is a \(\mu\)-opioid receptor agonist and exerts potent analgesic effects. Although the onset of the analgesic effect of fentanyl is rapid, the duration of effect is relatively short. Therefore, repeated administration or constant rate infusion of fentanyl is generally used to maintain adequate analgesia. Although the duration of the pharmacological effect of fentanyl after first administration is short, the duration of effect is extended dramatically if the drug is administered for a longer time in humans [13]. However, delayed recovery from anesthesia and sustained respiratory depression after recovery from anesthesia are common when the drug is used repeatedly or for an extended period in humans [2, 7]. Therefore, perioperative fentanyl has been replaced by newly developed opioids, such as remifentanil, sufentanil and alfentanil, which are metabolized rapidly and have shorter elimination half-times [1].

Context-sensitive half-time (CSHT) is the time required for a 50% decrease in the central-compartment drug concentration (i.e., plasma drug concentration) after the termination of infusion [5]. In humans, CSHT of fentanyl is markedly prolonged when infusion duration exceeds 2 hr, suggesting fentanyl may be unsuitable for procedures lasting more than 2 hr. Although fentanyl has been used widely in dogs as described above, little information is available on CSHTs of fentanyl and safety of long-term infusion of fentanyl is not fully understood in dogs. In this study, we performed computer simulations to obtain CSHTs of fentanyl in dogs by using 2 published pharmacokinetic models [8, 10]. CSHTs of fentanyl according to a human pharmacokinetic model were used for comparative purposes [12].

Multi-compartment models were used to obtain the CSHTs of fentanyl. For instance, a 3-compartment model would be expressed as follows: 

\[
C(t) = A_1 e^{-\lambda_1 t} + A_2 e^{-\lambda_2 t} + A_3 e^{-\lambda_3 t},
\]

where \(C(t)\) is the central-compartment drug concentration, and \(A_1, A_2, A_3\) and \(\lambda_1, \lambda_2, \lambda_3\) are the coefficients and rate constants. We used the pharmacokinetic parameters published by Murphy et al. and Sano et al. for dogs (Murphy model and Sano model) [8, 10], and by Scott and Stanski for humans (Scott & Stanski model) [12], which are listed in Table 1. The central-compartment drug concentration was simulated according to a BET-type infusion during the drug infusion process. The BET-type infusion is an infusion regimen that can maintain the central-compartment drug concentration at a desired level by sequential adjustments of infusion rate. The details of the BET-type infusion have been described elsewhere [11]. The following equation was used to calculate the central-compartment drug concentration after completion of the BET-type infusion [5]:

\[
c(t) = V_i C_{pD} \left[ \sum_{j=1}^{n} \frac{k_{in}_j (1-e^{-t/T})}{\lambda_j} \right] + \sum_{j=1}^{n} k_{ji} \left( e^{-t/T} - e^{-t/T_i} \right)
\]

where \(t\) is the time elapsed after completion of the infusion; \(V_i\) is the apparent volume of the central compartment; \(C_{pD}\) is the desired drug concentration to be maintained during the drug infusion process; \(n\) is the number of compartments; \(A_i\) and \(\lambda_i\) are the coefficients and rate constants; \(T\) is the infusion duration; and \(k_{in}, k_{ij}\) and \(k_{ji}\) are the micro rate constants. We can simulate the decay of the drug concentration after completion of the infusion by using this equation. For instance, we can apply \(t=10\) min and calculate the drug concentration 10 min after the end of a 1 hr infusion, i.e. \(c(10\) min) when \(T=60\) min.

For estimation of the CSHTs at steady-state (i.e., drug concentrations in all the compartments are in equilibrium), \(T\) approached infinity, and the following equation was used:

\[
c(t) = V_i C_{pD} \left[ \sum_{j=1}^{n} \frac{k_{in}_j}{\lambda_j} \left( 1 - e^{-t/T} \right) \right] + \sum_{j=1}^{n} k_{ji} \left( e^{-t/T} - e^{-t/T_i} \right)
\]

where \(T\) is the steady-state time required for a 50% decrease in drug concentration in the central compartment after the end of the infusion.
As the CSHT.

In humans, it has been reported that the higher doses of fentanyl needed for intraoperative analgesia cause delayed recovery from anesthesia and prolonged respiratory de-

Table 1. Pharmacokinetic parameters

|               | Murphy model | Sano model | Scott & Stanski model |
|---------------|--------------|------------|----------------------|
| A₁(µg)       | 7            | 0.52       | 0.669                |
| A₂(µg)       | 0.76         | 0.15       | 0.0062               |
| A₃(µg)       | 0.29         | –          | 0.0015               |
| λ₁ (1/min)   | 0.561        | 0.18       | 0.67                 |
| λ₂ (1/min)   | 0.069        | 0.014      | 0.037                |
| λ₃ (1/min)   | 0.0051       | –          | 0.0015               |
| k₁₀ (1/min)  | 0.10         | 0.05       | 0.059                |
| k₁₂ (1/min)  | 0.213        | 0.09       | 0.373                |
| k₁₃ (1/min)  | 0.181        | –          | 0.174                |
| k₂₁ (1/min)  | 0.125        | 0.05       | 0.096                |
| k₃₁ (1/min)  | 0.0158       | –          | 0.0065               |
| Vᵣ(µl/kg)    | 0.12         | 1.5        | 13.0                 |

Fig. 1. Context-sensitive half-times (CSHTs) of fentanyl in dogs and humans by simulating BET-type infusions for 1 to 600 min. Solid and broken lines are the CSHT obtained from Murphy and Sano models [8, 10], respectively. Dashed line is the CSHT obtained from Scott & Stanski model [12]. The changes in CSHT in dogs (Murphy and Sano models) are small, and steady-state is reached when the infusion time exceeded 2–4 hr. In contrast, the CSHT in humans (Scott & Stanski model) substantially increases particularly with infusion times of 2 hr or more.
pression after recovery [2, 14]. Recently, newly developed opioids with shorter CSHTs, such as remifentanil, sufentanil and alfentanil [1], have been favored, because adequate analgesia is more easily obtained with minimal adverse effects. However, use of these opioids in dogs is limited by expense and the lack of available pharmacokinetic profiles for dogs. The present results suggest that the long-term infusion of fentanyl causes less delay in recovery and respiratory depression after recovery from anesthesia in dogs, even at the higher dose rates indicated for intraoperative use.

In conclusion, CSHTs of fentanyl in dogs are markedly shorter than those in humans. According to the CSHTs, a continuous infusion of fentanyl may be an ideal regimen in dogs, even if duration of infusion is extended.

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