NOTE *Pharmacology*

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 μ-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 Therefore, perioperative fentanyl has been replaced by newly developed opioids, such as remifentanil, sufentanil and alfentanil, which are metabolized rapidly and have shorter elimination half-times [1].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: $C(t)=A_1e^{-\lambda 1t} + A_2e^{-\lambda 2t} + A_3e^{-\lambda 3t}$, where C (t) is the central-compartment drug concentration, and A_i and λ_i (i=1, 2 or 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]:

$$c(t) = V_1 Cp_d \left\{ \sum_{i=1}^{n} A_i e^{-\lambda_i t} \left[e^{-\lambda_i T} + \frac{k_{10}}{\lambda_i}\left(1 - e^{-\lambda_i T}\right) + \sum_{j=2}^{n} \frac{k_{1j}}{k_{j1} - \lambda_i}\left(e^{-\lambda_i T} - e^{-k_{j1} T}\right) \right] \right\}$$

where t is the time elapsed after completion of the infusion; V_1 is the apparent volume of the central compartment; Cp_d is the desired drug concentration to be maintained during the drug infusion process; n is the number of compartments; A_i and λ_i are the coefficients and rate constants; T is the infusion duration; and k_{10}, k_{1j} and k_{j1} 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

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Table 1. Pharmacokinetic parameters

	Murphy model	Sano model	Scott & Stanski model
A_1[a)]	7	0.52	0.069
A_2[a)]	0.76	0.15	0.0062
A_3[a)]	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
k_{10} (1/min)	0.10	0.05	0.059
k_{12} (1/min)	0.213	0.09	0.373
k_{13} (1/min)	0.181	–	0.174
k_{21} (1/min)	0.125	0.05	0.096
k_{31} (1/min)	0.0158	–	0.0065
V_1[b)]	0.12	1.5	13.0

A_1, A_2, A_3: coefficients and λ1, λ2, λ3: rate constants in the equation: $C(t)=A_1e^{-\lambda 1t}+A_2e^{-\lambda 2t}+A_3e^{-\lambda 3t}$ where C (t) is the drug concentration at time t; K_{10}, k_{12}, k_{13}, k_{21}, k_{31}: micro rate constants; V_1: apparent volume of the central compartment; a) unit is *n*g/m*l* for Murphy model, kg/*l* for Sano model and 1/*l* for Scott & Stanski model; b) unit is *l*/*μ*g for Murphy model, *l*/kg for Sano model and *l* for Scott & Stanski model. Murphy model [8] or Scott & Stanski model [12] is three-compartment model. Sano model [10] is two-compartment model.

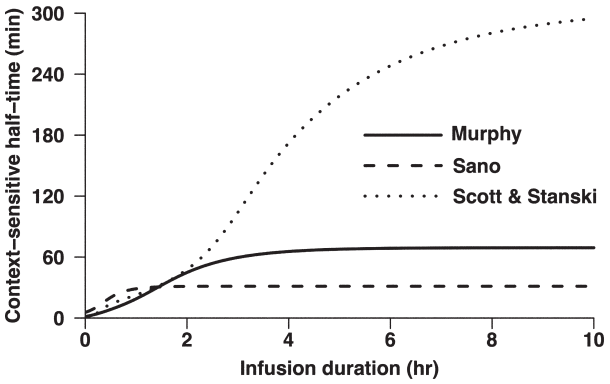

Fig. 1. Context-sensitive half-times (CSHTs) of fentanyl in dogs and humans by simulating BET-type infusions for 1 to 600 min. Solid and broken lines are the CSHT obtained from Murphy and Sano models [8, 10], respectively. Dashed line is the CSHT obtained from Scott & Stanski model [12]. The changes 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.

to calculate the central-compartment drug concentration at any time t [5]:

$$c(t) = V_1 k_{10} Cp_d \left\{ \sum_{i=1}^{n} \frac{A_i}{\lambda_i} e^{-\lambda_i t} \right\}$$

where abbreviations correspond to those used in the former equation.

For comparison of pharmacokinetic profile, conductance ratios were also calculated (i.e., k_{12}/k_{10} or k_{13}/k_{10}) [5].

All simulations were performed using the software Microsoft Excel 14.4.1 (Microsoft, Redmond, WA, U.S.A.). The central-compartment drug concentrations were calculated at 1 sec intervals. To simplify the calculation, the central-compartment drug concentration was maintained at 1 *n*g/m*l* (Cp_d=1 *n*g/m*l* in the equations) during the BET-type infusion process, and the time required for the central-compartment drug concentration to decrease from the concentration at the end of infusion (i.e., 1 *n*g/m*l*) to 0.5 *n*g/m*l* was determined as the CSHT.

Figure 1 shows the CSHTs in dogs and humans obtained in this study by simulating BET-type infusions for 1 to 600 min. The CSHTs increased as infusion duration increased in both dogs and humans. However, the changes in CSHT in dogs were small, and steady-state was reached when the infusion time exceeded 2–4 hr (Fig. 1). The CSHTs at steady-state were 69.2 and 31.3 min for the Murphy model and Sano model, respectively. In contrast, the changes in CSHT in humans were substantial, particularly with infusion times of 2 hr or more (Fig. 1). The CSHT at steady-state was 306.5 min in the Scott & Stanski model. Both conductance ratios were 1.8 in dogs, while the conductance ratio was 2.9 in humans.

The CSHTs of fentanyl in dogs were much shorter than those in humans, especially after 2 hr of infusion. This difference might have been due to pharmacokinetic differences in fentanyl metabolism between the 2 species. The rate constant for terminal elimination phase (λ2 in the 2-compartment model or λ3 in the 3-compartment model) of fentanyl has been reported as 0.014 and 0.0051 /min [8, 10], respectively, in dogs, while that in humans has been reported as 0.0015–0.0037 /min [9]. As plasma drug concentration decreases more rapidly when the rate constant for terminal elimination phase is higher, the higher rate constant in dogs would have contributed to the shorter CSHTs in dogs compared with humans.

Because the peripheral compartment acts as a reservoir for drugs infused for a long time, the relationship between the central and the peripheral compartments might have contributed to the results obtained in this study. The conductance ratio, k_{12}/k_{10} or k_{13}/k_{10}, indicates the speed of intercompartmental drug transfer. The greater conductance ratio in humans than dogs in the present study may explain the longer CSHTs in humans compared with dogs. A drug with a large conductance ratio that is distributed in the peripheral compartment returns to the central compartment quickly. Therefore, after cessation of long-term infusion of a drug with a high conductance ratio, the central-compartment concentration decreases slowly, because of rapid movement of the drug from the peripheral compartment to the central compartment. In contrast, the central-compartment concentration decreases rapidly after cessation of long-term infusion of a drug with a low conductance ratio, because the drug distributed in the peripheral compartment returns to the central compartment more slowly [5].

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-

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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