Title: DOSE-INDEPENDENT PHARMACOKINETICS OF FENTANYL.

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Introduction. Fentanyl is used as an analgesic in small doses (1-2 μg/kg) and as an anesthetic in very large doses (>150 μg/kg). Large doses have been administered as an intravenous bolus for the rapid induction of anesthesia.[1] It is important to know whether or not the pharmacokinetics of fentanyl distribution and elimination vary with dose size in order to predict the consequences and concentrations likely to be produced by various dosage regimens. Fentanyl is eliminated primarily by metabolism in the liver and saturation of biotransformation mechanisms has been described for other drugs.[2] It is difficult to justify the administration of very large bolus doses to volunteers and physically fit surgical patients and to examine basic pharmacokinetics under varying conditions of surgery. Therefore, we examined the pharmacokinetics of fentanyl (2.5 to 640 μg/kg) in dogs anesthetized with enflurane or pentobarbital. General anesthesia with controlled ventilation facilitated the maintenance of stable conditions throughout the experimental period.

Methods. Twenty-three mongrel dogs (10-20 kg) received succinylcholine (0.1 mg/kg) and atropine (0.1 mg/kg) iv and were anesthetized rapidly with 5% enflurane in O_2 (n=19) or pentobarbital (30 mg/kg, iv;n=4). After tracheal intubation, anesthesia was maintained with 1.5-2% enflurane in end-tidal gas or with intermittent doses of pentobarbital (10 mg/kg, iv). Mechanical ventilation with 98-100% O_2 provided normal $PaCO_2$ and pH. Lactated Ringer's solution was infused (12 ml.kg^{-1}.hr^{-1}) and blood removed for analysis was replaced with an equal volume of Plasmanate. Tritium-labeled fentanyl (^{3}H-F) was injected iv over 30 sec as a single dose (2.5-640 μg/kg) and femoral arterial blood samples (5-8 ml) were collected intermittently for 8 hours and analysed for unchanged ^{3}H-F.[3] Pharmacokinetic variables were calculated by standard methods based on non-linear least squares analysis of fentanyl concentration in plasma [F] vs time after injection. Values are expressed as means + SE and Student's t-test was used for group comparisons.

Results. Transient (0.5-6 min) small (0-10%) decreases in systolic blood pressure and heart rate occurred after fentanyl injection in some dogs with no apparent relationship to dose-size or type of anesthesia. Thereafter, hemodynamic values remained stable at normal levels, as did body temperature, acid base balance, and urine volume. The progressive decline of plasma [F] was best described by a tri-exponential equation: $[F]=Pexp^{-\pi t}+Aexp^{-\alpha t}+Bexp^{-\beta t}$. Pharmacokinetic variables are summarized in the Table. Except for the lowest fentanyl dose which produced plasma levels in late samples near the limits of the sensitivity of the analytical method, there was no dose-related difference in the pharmacokinetics of fentanyl in the enflurane anesthetized dogs. Although there was a statistically greater fentanyl clearance in dogs given the 64 μg/kg dose during pentobarbital than during enflurane anesthesia (Table), the range of values overlapped for these two groups and the difference between pentobarbital and enflurane anesthesia was not evident in dogs receiving the 6.4 and 640 μg/kg doses. This difference in clearance was marginally reflected in the elimination half-time.

Discussion. To date, mongrel dogs have proven to be suitable animal models for normal man in studies of the disposition of narcotic analgesics, including fentanyl.[3,4] The present study demonstrated no dose-dependent or substantial differences in the pharmacokinetics of fentanyl over a 256-fold dose range. Certainly there was no evidence of saturation of the biotransformation mechanisms primarily responsible for elimination of fentanyl.[3,4] Dose-independent kinetics facilitate the prediction of the consequences of different dosage regimens (variation in dose-size, infusion vs bolus dose, etc.). Of course, other factors (e.g. hemodynamics, liver function) may alter pharmacokinetics. In this study, only questionable differences in the disposition of fentanyl were evident between dogs anesthetized with enflurane or pentobarbital. In contrast, a larger distribution volume (19 l/kg), more rapid clearance (1161 ml/min), and a shorter elimination half-time (125 min) for fentanyl have been reported for 3 dogs anesthetized with nitrous oxide and pancuronium.[5] Therefore, the pharmacokinetics of fentanyl may differ in the presence of certain anesthetics.

References. 1) Kentor ML, Schwalb AJ, Lieberman RW: Rapid high dose fentanyl induction for CABG. Anesthesiology 53: s95, 1980.
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FENTANYL PHARMACOKINETICS IN DOGS

Dose (μg/kg)	n	Distribution Vol. (l/kg) Initial	Total	Clearance (ml.kg^{-1}.min^{-1})	Elimination Half-time (min)
Enflurane Anesthesia					
2.5	4	0.3±.05**	6.4±0.9*	31±2	147±26+
6.4	4	1.0±.17	10±1	38±5	197±36
64	7	1.2±.21	9.5±0.6	34±2	196±13
640	4	1.1±.07	9.4±0.3	41±2	163±20
Pentobarbital Anesthesia					
64	4	0.9±.21	8.7±0.2	41±1++	150±18+

**p<.02 vs other groups ++p<.05 vs enflurane,64 μg/kg
*p<.05 vs other groups +p<.10 vs enflurane,64 μg/kg