

Title : FENTANYL PHARMACOKINETICS IN MAN  
Authors : D.A. McClain, M.D. and C.C. Hug, Jr., M.D., Ph.D.  
Affiliation: Department of Anesthesiology, Emory University Medical School  
Atlanta, Georgia 30322

**INTRODUCTION.** Fentanyl (F) is considered to be a "short-acting" narcotic analgesic. However, prolonged and recurrent ventilatory depression has been reported in man. Studies in dogs suggest that the short duration of F action after single moderate doses is due to its rapid redistribution from brain to other tissues and that repeated or large doses lead to accumulation of F and ventilatory depression.<sup>1,2</sup> This study examined the pharmacokinetics of F in man in order to determine the applicability of conclusions from animal studies to humans.

**METHODS.** Six normal males (22-29 yrs) gave informed consent to this institutionally approved study. They weighed 65-85 kg, fasted before and during the study, received iv fluids (2 ml/kg/hr), and breathed O<sub>2</sub> for 45 min after fentanyl injection. Respiration, blood gases, blood pressure, ECG, and urine output were monitored. A 5 or 10 µg/kg dose of <sup>3</sup>H-fentanyl citrate (87 nCi/µg) was injected iv over 90 sec. Arterial plasma and urine were analysed for unchanged F and for total <sup>3</sup>H (i.e., F and its metabolites).<sup>1</sup> Pharmacokinetic variables were calculated using non-linear, least squares regression analysis.

**RESULTS.** F elimination from plasma was described by the equation:  $C_p(t) = P e^{-\pi t} + A e^{-\alpha t} + B e^{-\beta t}$ .  $C_p$  represents F conc. at any time (t) after injection. The mean kinetic variables  $\pm$  SEM for a 10 µg/kg dose in man are shown in the table along with data from dogs<sup>1</sup> for comparison. The rate constants were independent of dose and the intercepts proportional to dose. The initial decline of plasma F was rapid and attributable to its extensive uptake by tissues. Its apparent distribution volume ( $V_d$ ) averaged  $4 \pm 0.3$  L/kg and  $57 \pm 1\%$  of F in plasma was bound to protein at pH 7.3 (respiratory acidosis). The half-time for the ultimate elimination of F was  $3.6 \pm 0.2$  hrs; pharmacokinetic models of F disposition indicated that the rate-limiting step was its re-uptake from certain peripheral tissues (e.g., fat). Biotransformation of F was efficient; metabolites were present in plasma 1.5 min after injection and accounted for 56% of total <sup>3</sup>H by 60 min. Urine collected over 72 hrs contained only  $6 \pm 1\%$  of the dose as unchanged F and  $70 \pm 2\%$  as metabolites.

**DISCUSSION.** The pharmacokinetics of F in awake volunteers were very similar to those reported for anesthetized dogs (table).<sup>1</sup> The extensive uptake of F by tissues (large  $V_d$ ) and its prolonged elimination half-time indicate the potential for accumulation of F after large or repeated doses in man. It is likely that F accumulation will be associated with cumulative respiratory effects since

there appears to be a close correlation between plasma levels of F and ventilatory depression in man (figure), and accumulation of both F and ventilatory depression has been demonstrated in the dog.<sup>2</sup> The anesthesiologist should be aware of this potential for prolonged ventilatory depression from this "short-acting" narcotic analgesic. He should also recognize that hypoventilation from residual F may recur when the intensity of noxious stimulation decreases (e.g., after surgery).

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#### REFERENCES.

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2. Hug CC Jr., Murphy MR: Fentanyl disposition in cerebrospinal fluid and plasma and its relationship to ventilatory depression in the dog. *Anesthesiology* 50:342-349, 1979.
3. Harper MH, Hickey RF, Cromwell TH, et al: The magnitude and duration of respiratory depression produced by fentanyl and fentanyl plus droperidol in man. *J Pharmacol Exp Ther* 199:464-468, 1976.

Table. Pharmacokinetics of Fentanyl in Plasma

	n	P ng/ml	$\pi$ min <sup>-1</sup>	A ng/ml	$\alpha$ min <sup>-1</sup>	B ng/ml	$\beta$ min <sup>-1</sup>
Man	4	22.1 $\pm 4.8$	0.46 $\pm 0.05$	3.0 $\pm 0.8$	0.065 $\pm 0.008$	2.2 $\pm 1.1$	.0033 $\pm 0.0002$
Dog	4	8.4 $\pm 2.6$	0.34 $\pm 0.03$	2.4 $\pm 0.2$	0.028 $\pm 0.003$	0.60 $\pm 0.11$	.0039 $\pm 0.0006$

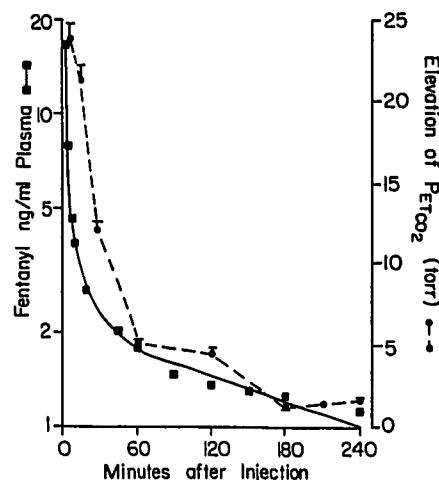


Fig. Comparison of fentanyl elimination from plasma and recovery from ventilatory depression in man.  $PETCO_2$  values adapted from data of Harper et al.<sup>3</sup>