Title: PHARMACOKINETICS AND DYNAMICS OF FENTANYL INFUSIONS IN CARDIAC SURGICAL PATIENTS.

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Introduction. While studying the hemodynamic changes associated with fentanyl (F) anesthesia and aortocoronary artery bypass (ACB) surgery, we noted that patients given a single bolus dose of 75 µg/kg became responsive following extracorporeal circulation (CPB). We therefore 1) examined the kinetics of F elimination during ACB surgery and 2) devised infusion regimens to maintain F levels adequate for ACB surgery.

Methods. Eighteen patients (40-65 years, 65-100 kg, 3 females) scheduled for elective ACB surgery gave their consent to this study as approved by the Human Investigations Committee. They received their usual morning doses of propranolol (20-80 mg, po) and nitroglycerin (1 inch topically), and also diazepam (0.15 mg/kg, po), morphine (0.1 mg/kg, im) and scopolamine (0.3 mg/70 kg, im). After preparations for anesthesia and monitoring, the patients breathed 100% oxygen continuously for the duration of anesthesia. Three groups of 6 patients each received F either as a single dose of 75 µg/kg at a rate of 300 µg/min or as a loading infusion (2.4 $\mu g.kg^{-1}.min^{-1}$ for 20 min) along with a continuous maintenance infusion of either 0.15 ("low") or 0.3 ("high") $\mu g.kg^{-1}.min^{-1}$ for the duration of anesthesia. Some patients exhibited decreased ventilatory compliance just before becoming unconscious, and received 20 mg succinylcholine to facilitate ventilation and subsequently to allow verification of unconsciousness. With unconsciousness, pancuronium (0.1 mg/kg, iv) was administered. No additional muscle relaxant was used, and recovery of neuromuscular function before the end of CPB was verified by ulnar nerve stimulation. If the patient responded to surgical stimulation by eye opening or movement, he received diazepam (5 mg iv, prn) and the F infusion was maintained at the same rate. Fentanyl concentrations [F] in arterial plasma were determined by radioimmunoassay. Pharmacokinetic parameters were determined by conventional methods and data are expressed as the mean ± SE. Student's t-test was used for group comparisons.

Results. [F] at specific points during anesthesia and ACB surgery are shown in Table 1. The times of each "milestone" did not differ for the 3 groups and the mean number of minutes after the start of F administration is shown for all 18 patients. Notable observations for patients given a single 75 µg/kg dose are 1) the 42% decline in F at the start of CPB, 2) the stability of [F] thereafter during CPB, and 3) the fact that the [F] was uniformly less than 9 ng/ml and all 6 patients became responsive before the end of surgery. In contrast, each of the 6 patients given the high maintenance infusion had [F] greater than 17 ng/ml throughout the surgical procedure and none became responsive until 4±0.6 hr after surgery when [F] averaged 9±1 ng/ml. One-half the patients receiving the low infusion rate required diazepam after hypothermic CPB. Good hemodynamic stability was present in the high infusion group, whereas some patients in each of the other two groups required other drugs to suppress cardiovascular responses to noxious stimulation. The rate of F elimination was the same in all 3 groups (Table 2). All patients were extubated the morning after surgery with the exception of 3 in the low infusion group that were given diazepam after CPB.

Discussion. There appears to be a close relationship between plasma [F] and F effects.[1] The occurrence of responsiveness with the progressive decline of [F] is to be expected and was evident in all patients when less than 10 ng/ml was present. Under our conditions of ACB surgery, [F] above 17 ng/ml suppressed responsiveness; this level is close to that producing a maximal reduction of enflurane MAC in dogs.[2] A relatively stable [F] was maintained by a continuous infusion of F after an initial loading dose without accumulation of excessive [F] nor marked prolongation of recovery of ACB patients. The loading dose is necessary to shorten the time of approaching the desired stable [F] and may also be useful in suppressing responses to the intense noxious stimulation at the beginning of ACB operations. Regardless of dosage regimen, F elimination in patients undergoing CPB is much slower than that in volunteers ($t_{\frac{1}{2}\beta}$=3.7 hrs) and "non-CPB" patients ($t_{\frac{1}{2}\beta}$=3.3 hrs).[1,3] This appears to be due to an increased distribution volume (Vd) and a diminished clearance (Cl) of F (Table 2 vs volunteers Vd=4 l/kg and Cl=13 $ml.kg^{-1}.min^{-1}$).[1]

References.

1) McClain DA, Hug CC Jr: Intravenous fentanyl kinetics. Clin Pharmacol Ther 28: 106-114, 1980.
2) Murphy MA, Hug CC Jr: The anesthetic potency of fentanyl in terms of its reduction of enflurane MAC. Anesthesiology 55: A249, 1981.
3) Koska AJ, Romagnoli A, Kramer WG: Effect of cardiopulmonary bypass on fentanyl distribution and elimination. Clin Pharmacol Ther 29: 100-105, 1981.

TABLE 1. PLASMA [F] (ng/ml ± SE)

Event (min ± SE)	Single Dose	Continuous Infusion Low	Continuous Infusion High
Peak [F] (21±0.3)	83±10	77±5	67±5
1'Before CPB (63±2)	16±3	17±1	27±1**++
Max. Cold (83±3)	9±1	15±1**	20±1**++
15'After CPB (165±7)	9±1	13±1*	19±1**++
End Oper. (206±9)	7±0.3	16±1**	23±1**++
At 24 hours	-	1.4±0.3	2.3±0.3+

*p<0.5 vs single dose
**p<0.001 vs single dose
+p<0.5 vs low infusion
++p<0.001 vs low infusion

TABLE 2. F PHARMACOKINETICS

	Single Dose	Continuous Infusion Low	Continuous Infusion High
Total dose (µg/kg)	75	84±3*	107±2**++
$t_{\frac{1}{2}\beta}$ (hrs)	11±2	12±1	11±1
Vd (l/kg)	9.0±0.9	7.5±0.8	7.3±0.7
Cl ($ml.kg^{-1}.min^{-1}$)	7.5±1.5	7.3±0.9	8.0±0.2