Title: PROLONGED RESPIRATORY DEPRESSION IN CARDIAC SURGERY PATIENTS: THE CONTRIBUTION OF FENTANYL

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Introduction. Respiratory depression and inability to sustain unassisted ventilation may have many causes after cardiac surgery. Residual anesthetic or postoperative analgesic and sedative drugs may play a role; surgery may exacerbate preexisting pulmonary disease. Congestive heart failure or neurologic damage may preclude extubation. With the acceptance of the high-dose (50-150 ug/kg) fentanyl (FE) technique, the incidence of respiratory depression on the day after surgery (POD1) has seemed to increase in our intensive care unit. This study was designed to separate the contribution of FE from other factors as an aid to designing an anesthetic regimen with desirable, predictable postoperative qualities.

Methods. After IRB approval and patient consent, 95 consecutive male patients having cardiac surgery under high-dose FE anesthesia were studied. FE dose was left to the discretion of the anesthetist who recorded doses and times. Total diazepam was limited to 15 mg, and thiopental to 500 mg. Ventilatory weaning and extubation (EXT) were performed by the usual clinical criteria including adequate spontaneous gas exchange, alertness, hemodynamic stability and time between 6AM and 5PM. Demographic data was gathered on all patients including any preoperative pulmonary dysfunction (PD) (>70 pk yrs, FEV_1 <60% of FVC, room air pO_2 <65). Patients in whom EXT was delayed by hemodynamic, neurologic or logistical factors or those receiving >40mg morphine for postoperative analgesia were excluded from further analysis. The others were divided into 2 groups: GRP 1) those successfully extubated before 10AM on POD1, GRP 2) those still ventilated because of drowsiness and hypercarbia.

FE concentrations in patient serum were measured by radioimmunoassay every 4hr from the end of surgery until EXT. A one-compartment pharmacokinetic model was fit to the postdistribution data by nonlinear regression. The FE concentration at 10AM on POD1 ($C10_{am}$) was calculated for each patient using the regression equation. In addition, the concentration at EXT (CE) was calculated by interpolation between measured data points. FE concentrations were compared between groups by analysis of variance, with $p<.05$ considered significant. For patients with and without PD separate logistic regression analyses of $C10_{am}$ vs. EXT were performed using the equation:

$$P = 1 - \frac{C10am^{\gamma}}{C10_{am}^{\gamma} + C50^{\gamma}}$$

where P=the probability of EXT by 10AM; C50=FE concentration below which 50% of patients could be successfully extubated; and γ describes the regression slope. In addition, C25, C75 and C90 (FE levels below which 25, 75 and 90% of patients could be extubated) were calculated from the logistic regressions. Dose simulations were performed with individual patient regression equations.

TABLE 1. Fentanyl Concentrations (ng/ml) Permitting Extubation

	N	C25	C50	C75	C90	γ
No PD	50	5.63	4.08	2.96	2.14	3.41
PD	18	5.51	2.48	1.12	0.50	1.38

Results. Patients in GRP 1 and 2 did not differ in age, weight, mean FE dose (98ug/kg) or mean dose of morphine (14mg). $C10_{am}$ was 2.8 $\pm$ 1.15 (SD) ng/ml in GRP 1 vs. 3.64 $\pm$ 1.46 in GRP 2 ($p=.0001$). CE did not correlate with age, but patients with PD had lower CE's than patients without: 2.42 $\pm$ .93 vs. 3.11 $\pm$ 1.23 ng/ml ($p<.05$). Results of the logistic regression analysis are shown (Table 1). The projections in Table 2 arise from simulating each patient's $C10_{am}$ on POD1 after different doses given at 8AM on the day of surgery. For FE given at other times, these doses should be adjusted by approximately 4%/hr to account for FE elimination ($T_{1/2}$ = 11-12 hrs). $C10_{am}$ is then related to the probability of EXT using the appropriate logistic regression.

TABLE 2. Probability of Extubation

	Fentanyl Dose (ug/kg)					
	50	75	100	125	150	200
No PD	.97	.90	.81	.71	.62	.47
PD	.77	.67	.58	.51	.46	.37

Discussion. This study provides important pharmacodynamic information on FE after cardiac surgery. The calculated C50's are conservative in that GRP 1 patients were extubated at FE levels slightly higher than $C10_{am}$. C75 in patients without PD agrees very closely with the FE level at extubation in a small previous study (1). At this level patients have normal $\dot{V}_E$ but 50% reduced CO_2 response (2,3). Patients with PD exhibited a lower C50 and more shallow slope (γ) of the logistic regression, suggesting impaired CO_2 elimination when narcotized, and a more heterogeneous response. The difference in $C10_{am}$ between GRP 1 and 2 patients would suggest that excessive FE level was responsible for delayed EXT in GRP 2. Since FE dose was identical in GRP 1 and 2, the explanation must be sought in other factors (e.g., pharmacokinetics). Table 2 applies the analysis developed here to the fundamental clinical question of outcome after doses of FE in current use. In patients without PD 75-100ug/kg given for AM surgery should permit EXT in 80-90% of patients the following morning. In patients with PD, doses should be reduced or a longer period of mechanical ventilation accepted.

References.

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2. Cartwright P, et al. Anesth Analg 62:966, 1983.
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