TITLE: COMPARATIVE PHARMACODYNAMICS OF FENTANYL AND ALFENTANIL USING THE EEG

AUTHORS: J.C. Scott, M.D. and D.R. Stanski, M.D.

AFFILIATION: Departments of Anesthesia and Medicine, (Clinical Pharmacology), Stanford University Medical Center, Stanford, CA 94305 and Palo Alto Veteran's Administration Medical Center, Palo Alto, CA 94043

Alfentanil has been reported to have a quicker onset of effect than fentanyl following equipotent bolus doses;[1] yet fentanyl has similar distribution kinetics and is more lipid soluble.[2,3] This study examines onset of effect using the EEG as a continuous quantifiable measure of effect.[4] The EEG response to alfentanil is similar to that of fentanil (Fig. 1). With EEG power spectral analysis to quantitate effect and simultaneous serum narcotic concentrations to provide pharmacokinetic information, pharmacodynamic modelling concepts are used to compare the onset of effect and estimate brain sensitivity to each narcotic.

Methods. After institutional approval and informed consent, 27 ASA I or II male patients were divided into Fentanil (N=13) or Alfentail (N=14) groups. Ages and weights were similar. The protocol for both groups was identical except as noted. No premedication was given. After line placement, the baseline EEG was recorded for 5 min. The narcotic was infused IV (fentanyl 150 mcg/min, alfentanil 1500 mcg/min) until delta waves appeared in the EEG (Fig. 1, Stage 3). Frequent arterial blood samples were drawn during and after infusion. EEG recording continued until the patient was alert and the EEG returned to baseline. Narcotic serum concentrations were determined by radioimmunoassay. The EEG was recorded on magnetic tape for off-line computer power spectral analysis and spectral edge calculation (frequency below which 95% of the EEG power is located).[5]

Data Analysis. Using non-linear regression spectral edge measurements were related to serum narcotic concentrations with this pharmacodynamic model: $SE(t) = E_o - E_{max} \cdot Ce(t)^{\gamma}/[IC_{50}^{\gamma} + Ce(t)^{\gamma}]$; where SE(t) = spectral edge (Hz) at time t; E_o (Hz) = baseline spectral edge; Emax (Hz) = maximum decrease in spectral edge due to the narcotic; γ is a power function (no dimension); Ce(t) is the concentration in the effect compartment at time t. Because the effect lags behind the narcotic levels, the model incorporates an effect compartment.[6] $T_{1/2}$Keo (half-time of equilibration between blood and effect site concentrations) quantitates the magnitude of the temporal lag (or hysteresis).

Results. The average total doses (mg) were: fentanyl 1.03 ± 4.7 and alfentanil 6.54 ± 1.78. Alfentanil patients lost responses and became apneic sooner than fentanyl patients but required a shorter period of assisted ventilation and were alert sooner.

Fig. 2 shows typical time courses for the narcotic levels and spectral edge responses. Note that fentanyl has a delayed onset and a delayed peak effect compared to alfentanil. Note that the axis for the spectral edge is inverted. $T_{1/2}$Keo was significantly shorter for alfentanil.

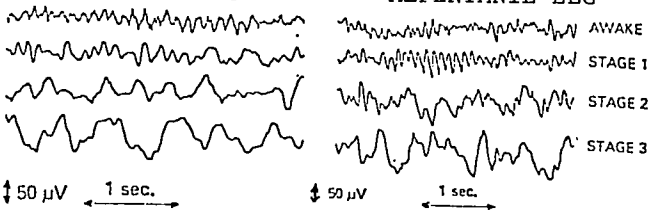
Discussion. Using the EEG as a continuous, quantifiable measure of narcotic effect, this study demonstrates significantly less time lag in onset of effect for alfentanil, thus substantiating clinical reports. Other measures of narcotic effect (analgesia, respiratory depression) might well have similar time courses. We attribute alfentanil's shorter $T_{1/2}$ Keo to less non-specific binding in the CNS compared with fentanyl,[3] as penetration of membranes (related to lipid solubility) does not appear rate limiting, nor do receptor events appear to be rate limiting.[7] By IC_{50} estimates (steady state sensitivity to the narcotics based on EEG slowing), alfentanil is about 70 times less potent than fentanyl. This contrast with published potency differences of alfentanil 3-10 times less potent than fentanyl. Bolus dose potency testing that ignores the concentration-effect hysteresis may lead to underestimating potency of the more slowly equilibrating drug.

Mean Pharmacodynamic Parameter Estimates (± S.D.)

	γ (-)	E_o (Hz)	E_{max} (Hz)	IC_{50} (ng/ml)	$T_{1/2}$ Keo (min)
Fentanyl N=13	4.3 (1.5)	19.1 (2.0)	12.2 (4.3)	6.7 (3.1)	5.4 (1.5)
Alfentanil N=14	4.8 (2.3)	18.6 (5.5)	13.2 (4.5)	450.2 (191.0)	1.1 (0.3)
	NS	NS	NS	***	***

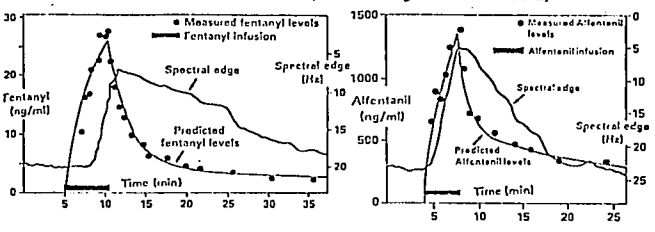
*** p < .001, NS = not significant

FIG 1. EEG RESPONSES TO FENTANYL & ALFENTANIL



Awake - mixed alpha (8 - 13 Hz) and beta (> 13 Hz) activity
Stage 1 - slowing with alpha spindles
Stage 2 - more slowing, theta activity present (4 - 7 Hz)
Stage 3 - maximal slowing, delta waves present (< 4 Hz) with high amplitude.

FIG 2. NARCOTIC SERUM CONCENTRATIONS AND SPECTRAL EDGE VS. TIME. (note: spectral edge axis inverted)



References.
1. Brown JH, et al. Br J Anaesth 52:1101, 1980
2. Bower S, et al. Br J Anaesth 54:871, 1982
3. Stanski DR, et al. Anesthesiology 57:435, 1982
4. Scott JC, et al. Anesthesiology 59:A370, 1983
5. Rampil J, et al. Anesthesiology 53:S12, 1980
6. Sheiner LB, et al. Clin Pharm Ther 25:358, 1979
7. Leysen JE, et al. Eur J Pharmacol 87:209, 1983