Subject: PHARMACOKINETIC ANALYSIS OF FENTANYL ADMINISTERED BY A COMPUTER CONTROLLED INFUSION PUMP

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Introduction: Computer controlled infusion pumps (CCIPs) offer the theoretical capability of maintaining constant and predictable drug concentrations in the blood, as well as the capability of adjusting the steady state drug concentration in response to changing anesthetic requirements. CCIPs require a mathematical model of drug behavior to achieve these goals. Available published parameters for these pharmacokinetic models are derived from multicompartmental analysis of drug redistribution and elimination following either a bolus injection or brief zero-order infusion. The pharmacokinetic parameters of fentanyl when infused in the exponentially declining manner required by CCIPs may not be, a priori, identical to those describing fentanyl kinetics following a bolus or zero-order infusion. We studied the pharmacokinetics of fentanyl delivered by CCIP, and compared the resulting pharmacokinetic parameters with those of published conventional pharmacokinetic studies.

Methods: After institutional review board approval and informed consent, we studied 11 patients undergoing a variety of procedures requiring general anesthesia. Their ASA status ranged from 1 to 4. Ten of the patients were women. The mean age was 57 (± 12 SD) years. The mean weight was 63 (± 15 SD) kilograms.

The CCIP was a highly modified version of the Computer Assisted Continuous Infusion pump developed by Alvis, et al.[1] The pharmacokinetic model used by the CCIP was the three compartment model of fentanyl described by McClain and Hug.[2] Blood samples were collected at 1 minute intervals for 10 minutes during the initial infusion period, then at increasingly longer intervals, for an average of 460 minutes per patient (range 80 to 1097 min). After any change in target levels, samples were drawn every minute for several minutes. Target fentanyl levels were chosen by the attending anesthesiologists and varied according to patient response and anesthetic requirements. We collected 321 blood samples, an average of 29 samples per patient (range 20 - 37). The serum was separated from the blood and frozen until the fentanyl was assayed by RIA. The lower limit of detection was 0.25 ng/ml.

The CCIP changed its infusion rate every 15 seconds to maintain the target level. At each 15 second interval the CCIP recorded on diskette the infusion rate and volume of drug already infused. Pharmacokinetic analysis was done using MKMODEL,[3] a non-linear regression program. MKMODEL was modified to incorporate the infusion file as the input to the pharmacokinetic algorithm. Two and three compartment fits were obtained for each patient. MKMODEL was further modified to compute two and three compartment fits on the pooled blood levels from all 11 patients. The fitting algorithm matched each patient with the exact infusion regimen used for that patient's anesthetic. We compared the parameters derived from our pooled data with several published parameter sets. We calculated the precision (average [absolute error / measured level]), bias (average [error / measured level]), and ratio (average [measured / predicted level]) for each parameter set (the error being the difference between the predicted and measured levels). The precision estimates the quality of the fit (0% = perfect fit), while the bias and ratio are estimates of systematic under or over prediction.

Results: Individual fits were well described by a three compartment model. The parameters derived from the pooled data also fit individual patients well, and overall described the 11 patients far better than the averaged parameters from the individual fits. Table 1 lists the parameters derived from the three compartment analysis of the pooled data ("Shafer"), as well as the published parameters of McClain,[2] Scott,[4] and Hudson.[5] Table 1 also lists the precision, bias, and measured/predicted ratios obtained by applying each parameter set to our patients' measured blood levels. Although the parameters of McClain and Hug were used to control the infusion pump, they poorly described the measured blood levels. The parameters of either Scott or Hudson are similar to the parameters we obtained by fitting the measured blood levels. Figure 1 shows a representative fit of our pooled parameters to an individual patient's measured levels. This patient had the median precision of all the patients.

Discussion: We have demonstrated that pharmacokinetic parameters can be obtained from analysis of the concentration versus time curves of patients receiving drug by CCIP, despite the complexity of the infusion function. The ability to calculate pharmacokinetics from such complex infusion schemes is novel. Our parameters appear to be better than those of McClain and Hug in describing the behavior of fentanyl when given by CCIP, and appear to be at least as good as the parameters of Scott and of Hudson. With optimal pharmacokinetic parameters the CCIP will become a powerful method of administering i.v. anesthetics.

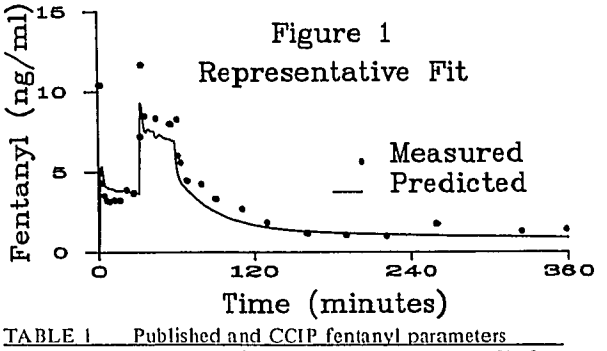

TABLE 1 Published and CCIP fentanyl parameters

Parameter	McClain	Scott	Hudson	Shafer
t 1/2 alpha (min)	1.61	1.02	2.10	0.96
t 1/2 beta (min)	12.63	18.73	31.00	20.60
t 1/2 gamma (min)	216.61	474.76	522.00	509.04
V central (liters)	26.91	12.70	22.37	6.87
V 2 (liters)	48.12	50.23	58.18	31.94
V 3 (liters)	195.32	295.07	290.06	261.03
Vdss (liters)	270.53	358.00	370.61	299.85
Cl central (l/min)	0.99	0.62	0.64	0.56
Cl 2 (l/min)	4.96	4.82	4.18	2.81
Cl 3 (l/min)	3.91	2.27	1.38	1.22
Precision (percent)	43	33	30	27
Bias (percent)	-33	-18	-17	10
Ratio (meas/pred)	1.84	1.40	1.38	1.00

1. Alvis, J.M., et al: IEEE Tran Biomed 32:323-329, 1985
2. McClain, D.A., Hug C.C.: Clin Pharm Ther 28:106-114, 1980
3. Holford, N: MKMODEL Users Manual, Elsevier, 1986
4. Scott, J.C., Stanski, D.R.: J. Pharm Exp Ther 240:159, 1987
5. Hudson, R.J., et al, Anesthesiology 64:334-338, 1986