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Pharmacokinetics of Fentanyl Administered by Computer-controlled Infusion Pump

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Fentanyl was administered to 21 patients using a computer-controlled infusion pump (CCIP) based on a pharmacokinetic model. Eleven of the patients were dosed according to the pharmacokinetics described by McClain and Hug, and ten of the patients were dosed according to the pharmacokinetics described by Scott and Stanski. The authors measured the difference between the measured arterial fentanyl concentrations and the concentrations predicted by the CCIP for each pharmacokinetic parameter set. The median absolute performance error (MDAPE) in patients dosed according to McClain and Hug's parameters was 61%, and the MDAPE in patients dosed according to Scott and Stanski's parameters was 33%. The population pharmacokinetics in these 21 patients were analyzed using a pooled data technique. The pharmacokinetics of fentanyl in this population showed a smaller central compartment volume and a more rapid initial distribution half-life than previously estimated for fentanyl. The derived pharmacokinetic parameters described these patients well and also predicted the observed fentanyl concentrations from four previously published fentanyl studies with reasonable accuracy. Comparison of the parameters used by the authors with those of McClain and Hug demonstrated that dosing regimens designed from pharmacokinetic models can be fairly accurate at the times sampled in the original study but may not be accurate at time points not sampled in the original research. The authors concluded that although the pharmacokinetics of fentanyl administered by CCIP are the same as the pharmacokinetics of fentanyl administered by a bolus or constant rate infusion, a pharmacokinetic study using a CCIP may be particularly effective at characterizing the most rapid distribution pharmacokinetic parameters, and thus may provide parameters appropriate for subsequent use in a CCIP. (Key words: Anesthesia: computer assisted. Anesthetics, intravenous: fentanyl; infusion. Equipment: infusion pump. Pharmacokinetics: population. Statistics: predictive performance.)

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ONE OF THE GOALS of pharmacokinetic research is improved drug dosing. After a bolus injection, the decline in the plasma concentration of most intravenous (iv) drugs used during anesthesia can be described by a polyexponential equation of the form:

$$\text{Concentration(t)}_{\text{bolus}} = Ae^{-\alpha t} + Be^{-\beta t} + Ce^{-\gamma t}$$

where t is the time since the bolus and A, α, B, β, C, and γ are the pharmacokinetic parameters. Because this curve describes how the plasma "disposes" of the drug over time, it is often called the "disposition function." The disposition function can be used to calculate infusion regimens that improve the accuracy of iv drug dosing.

Most people cannot mentally solve polyexponential equations. Instead, physicians administer iv drugs according to fixed regimens or titrate the drugs to perceived drug requirements based on feedback from the patient. Fixed dosing regimens suffer from lack of flexibility: for example, there is no easy method to return to a fixed dosing regimen if it is temporarily abandoned because of signs of drug overdose or underdose. Drug titration based on feedback works well for some classes of drugs, such as muscle relaxants, because the effect is easily measured. However, titrating opioids to clinical signs is far more difficult. If the patient appears lightly anesthetized, even very high opioid concentrations may not control hemodynamic responsiveness.[1] The patient who has received an overdose of an opioid may show no clinical signs of the overdose until the conclusion of the anesthetic when the patient fails to awaken promptly and breathe spontaneously. What is needed is a method of drug administration that allows the anesthesiologist to combine knowledge of drug pharmacokinetics and anticipated therapeutic ranges in the population with measures of drug effect in the individual patient to provide the best possible infusion regimen.

Based on work by Krüger-Thiemer,[2] Schwilden described a method of rapidly reaching and maintaining a constant plasma drug concentration using pharmacokinetic models.[3] Several research groups have since implemented such models in computer-controlled infusion pumps (CCIP).[4–6] The parameters used by the pharma-

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cokinetic models have been derived from conventional pharmacokinetic studies.

For many iv drugs used in anesthesia, there is wide variation in the parameters published by different investigators.[7] This study determines the optimal fentanyl pharmacokinetics for use in a CCIP. We first compared the CCIP performance using the fentanyl pharmacokinetic parameters described by McClain and Hug[8] with the CCIP performance using the parameters published by Scott and Stanski.[9] McClain and Hug studied fentanyl pharmacokinetics in seven awake, unanesthetized male volunteers. Scott and Stanski studied fentanyl pharmacokinetics in 20 healthy men undergoing general anesthesia for elective surgery.

We then derived yet another set of fentanyl pharmacokinetic parameters from the fentanyl concentrations obtained with our CCIP. Since these parameters were derived using a CCIP, they might, *a priori,* be better suited for use in a CCIP than parameters derived from a standard pharmacokinetic study where the drug is given as a single bolus or brief infusion.

Having derived fentanyl parameters from a CCIP study, our final goal was to compare these parameters with those derived from several previously published fentanyl studies. We used the same method as Maitre *et al.* in their retrospective analysis[10] of how accurately the alfentanil pharmacokinetic parameters derived from a NONMEM analysis[11] predicted the alfentanil serum concentrations from a previously published study by Ausems *et al.*[1] Our retrospective analysis analyzed how accurately the fentanyl pharmacokinetic parameters derived in this study predicted the observed concentrations from four previously published studies: McClain and Hug,[8] Scott and Stanski,[9] Hudson *et al.*,[12] and Varvel *et al.*[13] Hudson studied ten patients undergoing abdominal aortic repair with infrarenal cross-clamping, while Varvel studied eight patients undergoing major spinal surgery under general anesthesia. The pharmacokinetic parameters from each of these studies will be subsequently referenced as McClain's, Scott's, Hudson's, and Varvel's, respectively.

Methods

Part 1: Prospective Comparison of Two Published Fentanyl Parameter Sets

After institutional review board approval, we obtained informed consent to study 21 patients, ASA physical status 1–4, undergoing a variety of surgical procedures under general anesthesia. Seven of the patients were men. The mean age was 58 ± 11 (SD) yr. The mean weight was 69 ± 17 kg.

The patients were divided into two groups. For the first 11 patients, the CCIP was programmed with the fentanyl pharmacokinetic parameters reported by McClain and Hug.[8] These were chosen because previous reports suggested good CCIP performance using these pharmacokinetics.[4,5] For the next 10 patients, the CCIP was programmed with the pharmacokinetic parameters reported by Scott,[9] which were selected based on analysis of the first 11 patients.[14]

The anesthetic plan, including preanesthetic medication, induction drug, and use of a volatile agent, was formulated by the attending anesthesiologist. The only restriction imposed by the study was that the plan include a fentanyl infusion as part of the anesthetic maintenance. Following induction of anesthesia with thiopental, the investigator (S.L.S.), in concert with the attending anesthesiologist, selected a target fentanyl concentration based on the anticipated intensity of the surgical stimulus and the anesthetic technique (fentanyl/O_2, fentanyl/N_2O/O_2, and fentanyl/N_2O/isoflurane/O_2). The fentanyl concentration was increased or decreased during the anesthesia in response to the perceived anesthetic requirement. Toward the conclusion of the anesthetic, the CCIP infusion was discontinued sufficiently early to allow the predicted fentanyl concentration to decrease to 1.5 $ng \cdot ml^{-1}$ for emergence. In some instances, this was as early as 2 h before conclusion of the anesthetic.

Five of the patients underwent open heart surgery. Anesthesia for these patients was induced with fentanyl administered by the CCIP. The infusion was discontinued and the study terminated when the patient was placed on cardiopulmonary bypass. Four of the patients undergoing cardiopulmonary bypass were in the second group (CCIP programmed with Scott's fentanyl parameters.) The prebypass fentanyl pharmacokinetics for all five patients were similar to the pharmacokinetics observed in the patients not undergoing cardiopulmonary bypass.

Our CCIP consisted of an Apple II (first 14 patients) or a Toshiba MS-DOS computer (last seven patients) connected to an IMED 929 infusion pump with a serial interface. The algorithms were identical for the two computer systems and have been described previously.[15] The software was written by the author (S.L.S.) in Pascal for the Apple II and in C for the MS-DOS computer.¶ The pharmacokinetic algorithm in the software approximated the triexponential pharmacokinetics using Euler's numerical technique[15] with one iteration every 15 s. The software adjusted the infusion rate every 15 s and recorded these rates in a diskette file to provide a precise record of the infusion.

¶ This software, STANPUMP, is available at no charge from the author (S.L.S.). STANPUMP is written in C and runs on any 8088 compatible MS-DOS computer with a serial port. A mathematics coprocessor is not required. STANPUMP currently supports the following infusion pumps: IMED 929, IMED C2 protocol, Bard Chronofusor, and Harvard Pump 22.

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Arterial blood samples were collected at 0.5–1 min intervals for the initial 10 min of the infusion and then at increasingly longer intervals for an average of 372 min per patient (range, 80–1097 min). The shorter studies were usually on patients undergoing open heart operations where the study was terminated at initiation of cardiopulmonary bypass. The longest sampling times did not result from excessively long operations but rather from several patients being placed in the intensive care unit after the operation where arterial blood samples could be gathered postoperatively. After changes in target concentration, samples were drawn every minute for several minutes. A total of 603 blood samples were collected, with an average of 29 samples per patient. The serum was frozen until the fentanyl was assayed by radioimmunoassay using the method of Michiels *et al.*[16] The lower limit of quantitation was 0.25 $ng \cdot ml^{-1}$. The coefficient of variation between paired aliquots was less than 5% for fentanyl concentrations at and above 0.25 $ng \cdot ml^{-1}$.

CCIP performance was measured in terms of the concentration predicted by the pharmacokinetic model (C_P). Usually, the target concentration for the CCIP (C_T) was the same as C_P at the time of each blood sample. However, samples were also drawn when the CCIP was allowing the serum concentrations to decay to a new and lower C_T. At these times, C_T was less than C_P.

We defined the error as the difference between the measured concentration (C_M) and C_P. The errors associated with large values of C_P were of a greater magnitude than the errors associated with smaller values of C_P. Since the magnitude of the errors tended to be proportional to C_P, the percent performance error (%PE) was defined as:

$$\%PE = 100 \frac{C_M - C_P}{C_P}$$

The performance error measures the difference between the C_M and C_P in terms of C_P. This is useful because C_P is known during the course of the anesthetic. The performance for each parameter set for the population studied was defined as the median absolute performance error (MDAPE):

$$MDAPE = \text{median } \{|PE_i|, i = 1, \ldots, n\}$$

where n was the total number of samples for all subjects in the population. Previous investigators[6] have usually measured the performance in individual subjects and then expressed the performance as the average of the individual subjects' performances. We used the pooled data approach (*i.e.*, n = total number of samples for all subjects) to be consistent with our pooled pharmacokinetic analysis, as will be described in part 2 below.

The MDAPE is a measure of the inaccuracy of the CCIP. We chose the median, instead of the mean, absolute performance error as an overall measure of performance for three reasons:

1. It is clinically easy to interpret: half of the errors when using a CCIP will be smaller than the MDAPE, and half will be larger;
2. Since the absolute PEs are not normally distributed, the mean PE is difficult to interpret statistically, and useless clinically; and
3. A line of investigation by one of the authors (J.R.V.) indicates that the MDAPE tends to be minimized by nonlinear regression. This is not the case for the mean PE. It is attractive to measure the "goodness" of performance using a parameter that reflects the objective function used when deriving pharmacokinetic parameters.

The median performance error (MDPE) reflects the presence of systematic underdosing or overdosing by the CCIP. The MDPE was calculated as:

$$MDPE = \text{median } \{PE_i, i = 1, \ldots, n\}$$

where n was the total number of samples for all subjects.

We also calculated the 10th and 90th percentiles of the performance errors. These percentile ranks describe the dispersion of the PEs without assuming a normal distribution.

The MDAPE and MDPE and the 10th and 90th percentiles were used to compare the CCIP performance using the pharmacokinetic parameters reported by McClain with the CCIP performance using the pharmacokinetic parameters reported by Scott. The MDAPE and MDPE for each individual patient were calculated from the C_M and C_P values for each patient. The MDAPE was used to select the best, average, and worse results from each parameter set for graphic presentation.

Part 2: Derivation of Pharmacokinetic Parameters from Our Population

The observed fentanyl concentration *versus* time data and fentanyl infusion rates from part 1 were entered into MK-MODEL,** an extended least squares nonlinear regression program. We extensively modified MK-MODEL to process these regressions. First, biexponential and triexponential models were developed that could incorporate an infusion that changed every 15 s. These models were adapted from the equations derived by Maitre *et al.*[10] We fit each patient's concentration *versus* time data to both biexponential and triexponential models. However, some of the studies were as short as 80–

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120 min, while others were as long as 980–1097 min. MK-MODEL found biexponential and triexponential models for each of the patients, regardless of the length of the study. As expected, the fentanyl distribution and elimination half-lives of patients sampled for less than 2 h were invariably much shorter than the distribution and elimination half-lives of patients sampled for longer periods of time. It was not possible to obtain useful parameters by combining the pharmacokinetic parameters from individual patients into parameters that adequately described the observed fentanyl concentrations for all patients. We therefore modified MK-MODEL to simultaneously fit the observations for all 21 patients to a single "best" estimate of the pharmacokinetic parameters for the entire population.

The parameters estimated were the α, β, and γ hybrid rate constants; V_c (the volume of the central compartment); k_{21}; and k_{31} (the rate constants describing the return of drug from the peripheral compartments to the central compartment). These parameters were chosen because they could be most rapidly converted into the additional parameters required by the equations derived by Maitre *et al.*[10] As in many pharmacokinetic analyses, the magnitude of the errors ($C_M - C_P$) was proportional to the magnitude of the predicted concentrations (C_P). Therefore, MK-MODEL essentially minimized the percent error rather than the absolute error (*i.e.*, the variance was model as being proportional to C_P^2). Using weighted error, rather than absolute error, is also consistent with the measures of performance described in part 1 above.

Three models were investigated to evaluate the relevance of body weight on fentanyl pharmacokinetics. In the first model (table 1), the volumes and clearances were not adjusted for weight. In the second model, the volumes and clearances were proportional to weight. In the third model, the volumes and clearances were modeled as constants plus a scalar × weight. The models were analyzed by comparison of log likelihoods. If the difference between −2 × the log likelihoods for each model exceeded $4(\sim\chi^2_{0.95}[1])$, the more complex model was considered preferable.

Part 3: Retrospective Analysis of Published Fentanyl Pharmacokinetic Data

The authors of four previous studies[8,9,12,13] generously provided us with their data on doses, fentanyl concentrations *versus* time, and patients' weights. We calculated how well the pharmacokinetic parameters derived in part 2 predicted the observed serum concentrations in each of these studies. All four previously published studies used arterial blood samples to characterize the rapid distribution pharmacokinetics.

We first determined the representative pharmacokinetic parameters from each of the previous studies. Most pharmacokinetic parameters are not normally distributed among patients. This is particularly true of hybrid parameters, such as half-lives, which reflect complex interactions of underlying physiology. The parameters most likely to be normally distributed are those closest to the underlying physiology: the volumes (central and peripheral compartments) and clearances (metabolic and intercompartmental). Therefore, for each of the four previously reported studies, the mean volumes and clearances were calculated from the individual volumes and clearances.

McClain and Hug originally derived the pharmacokinetic parameters in terms of coefficients (A, B, and C) and hybrid rate constants (α, β, and γ). We transformed these parameters into volumes and clearances for each patient using standard pharmacokinetic equations.[17] We calculated the individual volumes and clearances for Scott and Stanski's patients from the individual rapid and slow distribution half-lives, the elimination half-life, the volume of the central compartment, and the volume of distribution at steady state. Hudson *et al.*[12] published the volumes and clearances for each patient, and the mean parameters. Varvel *et al.*[13] did not publish individual patient pharmacokinetic parameters. Therefore, we used

TABLE 1. Volumes and Clearances Derived for the Three Weight Models Estimated in Part 2: Summary of Derived Pharmacokinetic Parameters

Model	Unscaled	Weight-scaled*	Linear†	
Parameter Type	Constant	Scalar	Constant	Scalar
Volumes	(liters)	(l/kg)	(liters)	(l/kg)
Central	6.09	0.105	2.7	0.059
Rapid	28.1	0.446	12.5	0.273
Slow	228	3.37	101	2.21
Steady state	262	3.92	116	2.54
Clearances	$(l \cdot min^{-1})$	$(l \cdot kg^{-1} \cdot min^{-1})$	$(l \cdot min^{-1})$	$(l \cdot kg^{-1} \cdot min^{-1})$
Central	0.504	0.00838	0.223	0.00488
Rapid	2.87	0.0474	1.27	0.0278
Slow	1.37	0.0199	0.607	0.0133

* Weight-scaled model: volumes and clearances = scalar × weight.

† Linear model: volumes and clearances = constant + scalar × weight.

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MK-MODEL to refit each patient to a triexponential model. Varvel *et al.* conducted an iv and a transdermal fentanyl pharmacokinetic study on each patient.[13] Only the results of the iv pharmacokinetic study were used.

Two of the studies (McClain's and Hudson's) report the volumes and clearances as a function of weight ($l \cdot kg^{-1}$ and $l \cdot kg^{-1} \cdot min^{-1}$, respectively). The other two studies (Scott's and Varvel's) report parameters independent of weight. We calculated two parameter sets for each study: one independent of weight, and one in which all volumes and clearance were scaled to weight. The scaled volumes and clearances were calculated using the patients' weights published in the studies (McClain and Hudson) or those made available by the investigators (Scott and Varvel).

The analysis described above produced eight pharmacokinetic parameter sets (two from each previously published study). This yielded a total of 11 pharmacokinetic parameter sets, 8 from previously published studies and 3 derived from part 2 of this study. This also yielded five sets of observed serum fentanyl concentrations, four from previous studies and one from this study. We calculated the ability of each of the 11 pharmacokinetic parameter sets to predict the observed fentanyl concentrations from each of the five studies (*i.e.*, an 11×5 matrix). As explained in the "Appendix," for this analysis we chose RMS error as our performance measure. The RMS error was defined as:

$$\text{RMS error} = \sqrt{\frac{\sum_{i=1}^{n} PE_i^2}{n}}$$

where n was the number of samples in the entire study population.

Although RMS error is a statistically sound measure of performance, it is clinically uninterpretable. Since the MDAPE tends to be minimized when the RMS error is minimized, in part 1 we prospectively reported the performance of McClain's and Scott's fentanyl pharmacokinetic parameters in terms of the MDAPE. However, for this retrospective analysis, where we measured the ability of 11 pharmacokinetic parameter sets to predict the observed concentrations from five studies, we elected to use RMS error as the more statistically accurate, and hence more sensitive, performance measure. We still calculated and reported MDAPE in part 3 since it is clinically easy to interpret.

Results

Part 1: Prospective Comparison of Two Published Fentanyl Parameter Sets

Clinically, the CCIP performed satisfactorily. There were no intraoperative problems with either the hardware or software. There were no intraoperative complications from use of the CCIP. One patient required a single dose of 40 μg of naloxone at the conclusion of the anesthetic for a ventilatory rate of 4 breaths per min.

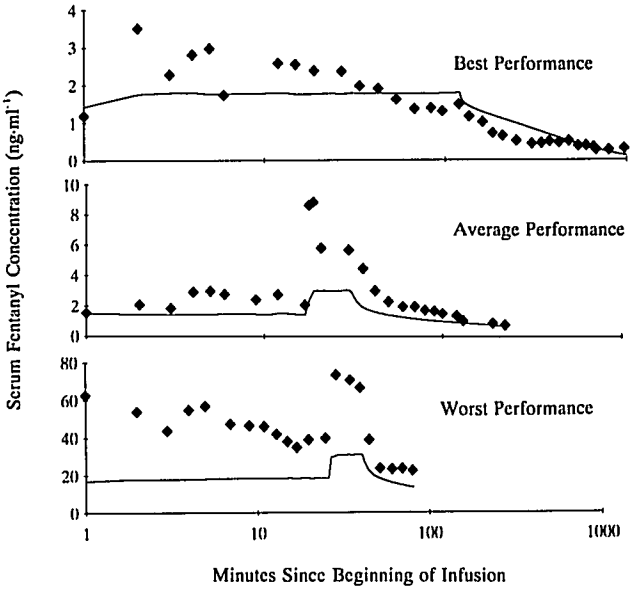

FIG. 1. The best, average, and worst CCIP performance in the 11 patients receiving fentanyl according to the pharmacokinetic parameters reported by McClain and Hug.[8] The diamonds are the measured concentrations, and the lines are the predicted concentrations.

The best, average, and worst performance seen in the 11 patients receiving fentanyl from a CCIP programmed with McClain's pharmacokinetic parameters are shown in figure 1. In each case, there was a marked initial overshoot, which decreased over time. Even in the best case, the observed concentrations generally exceeded the predicted concentrations over most of the anesthetic course. Figure 2 shows the performance errors over time for each of the 11 patients. The MDAPE for these 11 patients was 61%. The 10th, 50th (MDPE), and 90th percentiles for PEs were −19, +61, and +158%, respectively.

The best, average, and worst performance seen in the ten patients receiving fentanyl from a CCIP programmed with Scott's pharmacokinetic parameters are seen in figure 3. There was less overshoot than was seen with McClain's parameters. Figure 4 shows the performance errors over time for each of the ten patients. The MDAPE for these ten patients was 33%, and the 10th, 50th (MDPE), and 90th percentiles for PEs were −34%, +19%, and +81%, respectively.

Part 2: Derivation of Pharmacokinetic Parameters from Our Population

Table 1 presents the results of the population pharmacokinetic analysis of our 21 patients. Three models

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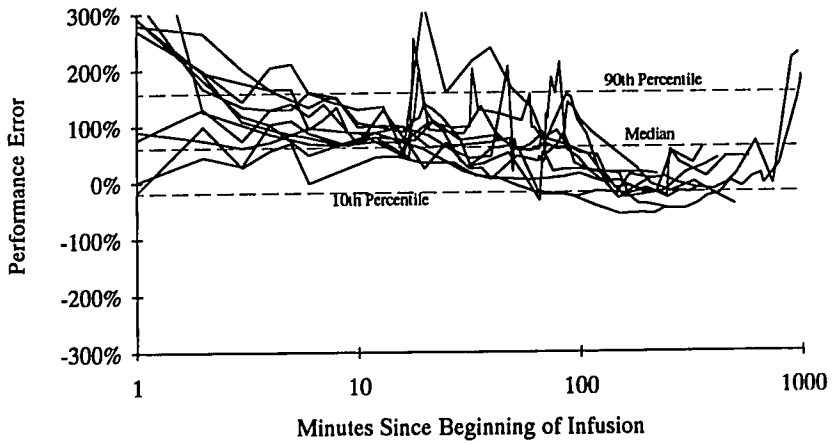

FIG. 2. The CCIP performance errors (in percent) over time for each of the 11 patients receiving fentanyl, according to the pharmacokinetic parameters reported by McClain and Hug.[8]

were analyzed: constant volumes and clearances, volumes and clearances scaled to weight, and volumes and clearances defined as constants plus a scalar × weight ("linear model"). The log likelihoods of the parameters estimated for each model were −1177, −1169, and −1112, respectively. Thus, the best model defined the volumes and clearances as a constant plus a scalar × weight. Although the differences in log likelihood between the best model and the other two models were statistically significant (difference in −2 × log likelihood >> 4), the actual improvement between the best model and the worst model in the estimation of the 594 observed fentanyl concentrations was quite small.

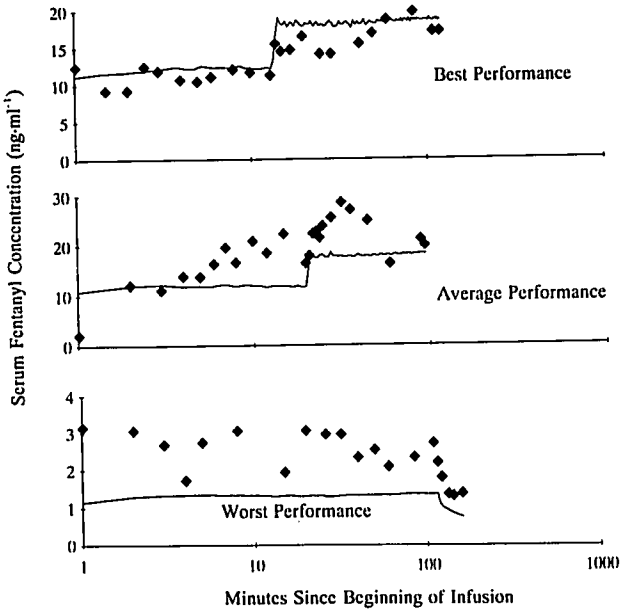

FIG. 3. The best, average, and worst CCIP performance in the 10 patients receiving fentanyl according to the pharmacokinetic parameters reported by Scott and Stanski.[9] The diamonds are the measured concentrations, and the lines are the predicted concentrations.

As will be explained below, the unscaled model was selected for the retrospective analysis and presentation of the data even though it was not quite as good a fit as the models that scaled volumes and clearances to weight. The best, average, and worst performance predicted for the unscaled model are seen in figure 5. Figure 6 shows the performance of these pharmacokinetic parameters in all 21 patients. Comparison of figure 6 with figures 2 and 4 shows the improvement in performance anticipated using these pharmacokinetic parameters. The MDAPE was 21% for these 21 patients, and the 10th, 50th (MDPE), and 90th percentiles for performance errors were −46, −13, and +30%, respectively.

PART 3: RETROSPECTIVE ANALYSIS OF PUBLISHED FENTANYL PHARMACOKINETIC DATA

When we calculated the ability of the 11 pharmacokinetic parameter sets to predict the observed fentanyl concentrations in this study and in four previous studies, there was no consistent pattern of parameter performance relative to weight scaling. For example, although our scaled model best predicted the serum fentanyl concentrations in our own study, it performed less well than the other models at predicting the observed concentrations from the previously published studies. The unscaled models generally predicted the fentanyl concentrations reported by McClain and by Scott better than the weight-scaled models. The reverse was true for the fentanyl concentrations reported by Varvel and by Hudson. Thus, we chose to present the model in which the volumes and clearances were unscaled because it was the simpler model, and there was no consistent trend favoring the more complex model with volumes and clearances scaled to weight. The unscaled pharmacokinetic parameters from the five studies, including those estimated in part 2 of this study, are presented in table 2.

Table 3 shows how well the observed fentanyl concentrations reported in each of the five studies were predicted

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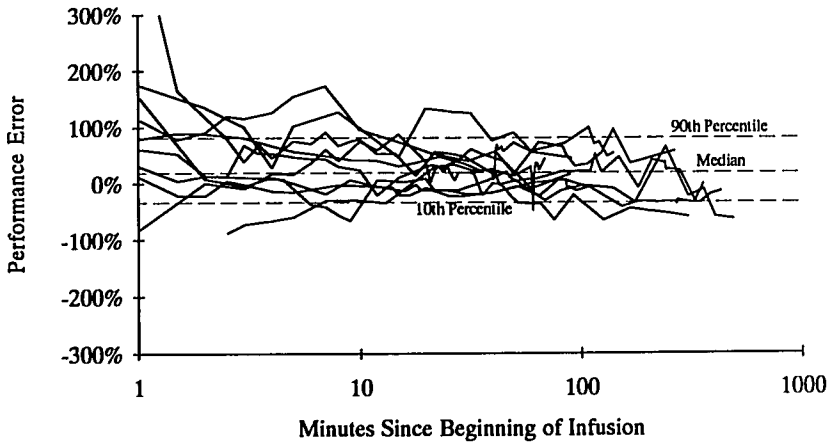

FIG. 4. The CCIP performance errors (in percent) over time for each of the 10 patients dosed according to the pharmacokinetic parameters reported by Scott and Stanski.[9]

by the fentanyl pharmacokinetic parameters from each of the studies. The results for study are presented in order of increasing RMS error, which was our measure of goodness for this analysis.

The pharmacokinetic parameters estimated in part 2 not only better predicted the concentrations observed in our 21 patients but also predicted the observed fentanyl concentrations in the studies of Scott and Varvel better than the parameters derived from those studies. Our parameters predicted the fentanyl concentrations observed by Hudson only slightly worse than Hudson's own published parameters. All parameter sets predicted the fentanyl concentrations observed by McClain quite well.

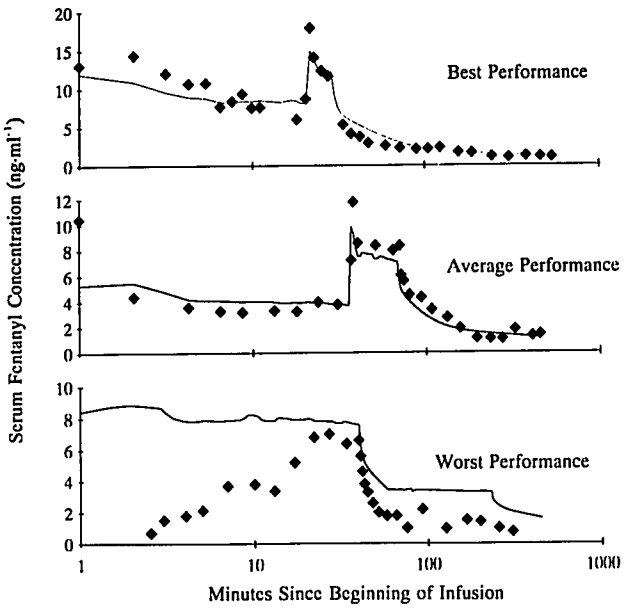

FIG. 5. The best, average, and worst estimated performance of all 21 patients, based on the concentrations predicted by the unscaled pharmacokinetic parameters derived in part 2. The diamonds are the measured concentrations, and the lines are the concentrations predicted by the derived pharmacokinetic parameters.

Discussion

PART 1: PROSPECTIVE COMPARISON OF TWO PUBLISHED FENTANYL PARAMETER SETS

The performance of a CCIP depends on the accuracy of the pharmacokinetic parameters programmed into it. In this study, the pharmacokinetics reported by Scott performed better than the pharmacokinetics reported by McClain using MDAPE as the measure of performance.

Numerous measures of predictive performance have been used in previous studies. Ausems *et al.*[6] and Maitre *et al.*[10] normalized their errors to measured concentration rather than to predicted concentration. This is less useful because the measured concentration is not known at the time of the operation. Additionally, nonlinear regression programs minimize the weighted errors (or, for extended least squares, the weighted errors plus the natural log of the predicted variance). Sheiner and Beal discussed whether the weights should be based on the predicted or measured concentrations.[18] They concluded that weighting by the measured concentration "is the worst of all methods and should be abandoned." Since it is attractive to use a measure of performance similar to the measure of goodness used when the pharmacokinetic parameters are derived, weighting the error by the predicted concentration is the proper approach.

PART 2: DERIVATION OF PHARMACOKINETIC PARAMETERS FROM OUR POPULATION

This is the first reported estimation of pharmacokinetic parameters from a CCIP study. This study presented three major difficulties in pharmacokinetic modeling:

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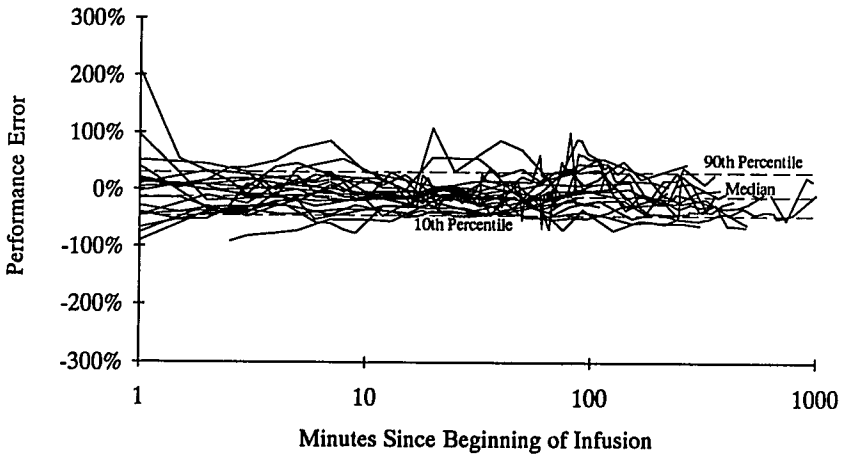

FIG. 6. The predicted performance errors (in percent) over time for each of the 21 patients based upon the unscaled pharmacokinetic parameters derived in part 2.

1. The data were collected on a variety of patients sampled for varying periods of time.
2. The protocol called for rapid sampling whenever C_T was changed. Since C_T was changed as required by the clinical situation, the timing and number of samples varied from patient to patient.
3. The complexity of the infusion regimen generated by the CCIP exceeded the capacity of available pharmacokinetic analysis programs.

Our MK-MODEL algorithms were able to address each of these difficulties.

The most challenging pharmacokinetic parameters to measure accurately are the rapid distribution half-lives and the volume of the central compartment. It is difficult to gather enough samples to characterize these high-frequency pharmacokinetic components in the minute or two that pass before slower processes control the serum concentrations. An advantage to this type of study is that we had another opportunity to gather more samples to characterize these very rapid pharmacokinetic components every time the CCIP raised the concentration. A conventional pharmacokinetic study might produce similar results if several boluses were administered that were spaced 20–30 min apart and accompanied by high-resolution arterial sampling.

We defined the pharmacokinetic parameters for our entire population by pooling the data and simultaneously

TABLE 2. Pharmacokinetic Parameters Estimated in the Current Study and Those Reported in Four Previously Published Studies

Parameters	Current Study	Hudson *et al.*[12]	McClain and Hug[8]	Scott and Stanski[9]	Varvel *et al.*[13]
Volumes (l)					
Central	6.09	22.4	26.6	12.7	8.71
Rapid	28.1	58.9	45.8	50.7	32.7
Slow	228	341	196	274	178
Steady state	262	422	269	337	219
Clearances ($l \cdot min^{-1}$)					
Central	0.504	0.769	0.883	0.574	0.715
Rapid	2.87	4.23	4.59	4.01	3.43
Slow	1.37	1.62	3.48	1.95	1.27
Half-lives (min)					
Rapid	0.82	2.00	1.73	1.22	1.00
Intermediate	17.2	28.0	13.5	21.9	18.2
Terminal	465	506	242	490	297
Hybrid rate constants (min^{-1})					
Rapid	0.845	0.346	0.400	0.567	0.694
Intermediate	0.0402	0.0247	0.0513	0.0317	0.0381
Terminal	0.00149	0.00137	0.00287	0.00141	0.00234
Micro rate constants (min^{-1})					
k10	0.0827	0.0344	0.0332	0.0452	0.0821
k12	0.471	0.189	0.172	0.315	0.394
k13	0.225	0.0723	0.131	0.154	0.146
k21	0.102	0.0719	0.100	0.079	0.105
k31	0.00600	0.00475	0.0177	0.00712	0.00715

The volumes and clearances are not scaled to weight.

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TABLE 3. The Ability of Five Fentanyl Pharmacokinetic Parameter Sets to Predict the Concentrations Measured in Five Different Studies

Observed Fentanyl Concentrations From:	Were Described by Pharmacokinetic Parameters From:	Performance Measures: RMS* Error (%)	Performance Measures: MDAPE† (%)
Current study	Current study	34	21
	Varvel *et al.*	38	22
	Scott and Stanski	56	33
	Hudson *et al.*	83	44
	McClain and Hug	113	59
Hudson *et al.*[12]	Hudson *et al.*	34	20
	Current study	37	32
	Scott and Stanski	38	26
	Varvel *et al.*	49	30
	McClain and Hug	93	33
McClain and Hug[8]	McClain and Hug	24	13
	Scott and Stanski	27	21
	Varvel *et al.*	32	19
	Current study	34	27
	Hudson *et al.*	42	25
Scott and Stanski[9]	Current study	36	26
	Scott and Stanski	42	24
	Hudson *et al.*	66	30
	Varvel *et al.*	49	27
	McClain and Hug	95	48
Varvel *et al.*[13]	Current study	49	28
	Varvel *et al.*	52	31
	Scott and Stanski	70	30
	Hudson *et al.*	81	40
	McClain and Hug	109	40

Comparison of fentanyl parameter sets is given in order of parameter performance.
* Root mean square error. See text for details.
† Median absolute performance error. See text for details.

fitting all data points to a single model. Pooling the data was necessary because of the different lengths of the individual cases and the variability of sampling between studies. This approach has sometimes been disparagingly referred to as the "naive" pooled data approach.[19] The disadvantage of this approach is that it combines the variability between subjects with the variability within subjects. Another method for analyzing population pharmacokinetics, NONMEM, characterizes the intrasubject and intersubject variabilities independently. Although our approach will not characterize the variance models as well as the NONMEM approach, our approach has produced robust estimates of the pharmacokinetic parameters for the population.

There are two main differences between the pharmacokinetic parameters derived during this study, and those from previously published studies (table 2): 1) Our central compartment volume is smaller; and 2) our rapid distribution half-life is shorter.

Since we rapidly sampled the arterial blood almost every time a new C_T was selected, we measured the rapid distribution pharmacokinetics several times for each patient. Our derived pharmacokinetic parameters have the smallest central volume and the most rapid initial half-life, which reflects the high-resolution sampling during the rapid distribution phase.

PART 3: RETROSPECTIVE ANALYSIS OF PUBLISHED FENTANYL PHARMACOKINETIC DATA

This portion of the study was modeled on a previously published alfentanil study by Maitre *et al.*[10] Unlike Maitre's study, we used a measure of performance, RMS error, which is closely related to the statistical definition of likelihood. The RMS error is thus statistically sound, although it is clinically uninterpretable.

The pharmacokinetic parameters derived from this study were particularly robust. Our parameters accurately predicted the observed fentanyl concentrations from four previously published studies. We did not intentionally select studies that we thought would be described by our pharmacokinetic parameters. Rather, we selected four well-conducted studies by prominent investigators where the fentanyl assay appeared to be carefully validated. The studies by Scott and by Varvel were conducted at the Palo Alto Veterans Administration Medical Center. Although our study was conducted at Stanford University Medical Center, the fentanyl concentrations from our study were assayed in the same laboratory used by Scott and by Varvel.

We were surprised that the pharmacokinetic parameters from this study predicted the fentanyl concentrations observed by Scott and by Varvel more accurately than the mean pharmacokinetic parameters reported in those studies. Calculating mean parameter values from individual patients, as was done in the previous studies, introduces bias because the calculation does not account for the different degrees of certainty with which the pharmacokinetic parameters are known in different individuals and assumes a normal distribution of parameters within the population. By contrast, the pharmacokinetic parameters from our study were derived by simultaneously fitting the entire population to a single model. This may explain why our parameters predicted the fentanyl concentrations observed by Scott and by Varvel better than the mean parameters derived from their patients.

All parameter sets predicted the fentanyl concentrations observed by McClain and Hug quite well. This is because there was very little variability in McClain's data: the plasma fentanyl concentrations in all of the volunteers deviated only slightly from an ideal triexponential decay. The other studies used patients undergoing general anesthesia. This suggests that some of the variability in the other studies was from alterations in fentanyl distribution

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and elimination introduced by the anesthesia and surgery over the course of the study.

We analyzed parameter sets that were scaled to weight and parameter sets that were not weight scaled. There was no overall pattern favoring either approach. This is partially a result of the range of weights studied: neonates probably will require less fentanyl than lumberjacks. If our data had included more patients at the extremes of weight, the analysis might have favored scaling volumes and clearances to weight. We were unable to examine other scaling methods, such as lean body mass or body surface area, because we did not record patient heights at the time of the study. Since there were no data favoring either the scaled or unscaled models, we chose the unscaled parameters as the simpler model. However, we suggest that these pharmacokinetics only be used in a CCIP for patients whose weight is within 1 SD of the mean weight (*i.e.*, 40–90 kg).

Because other investigators reported good CCIP performance with McClain's pharmacokinetic parameters,[4,5] we explored in detail the differences between McClain's pharmacokinetic parameters and the parameters estimated in part 2 of this study. We simulated the fentanyl concentrations that would have resulted from a 1,000-μg fentanyl bolus administered to a patient described by McClain's parameters and to a patient described by our parameters, and then "sampled" the serum fentanyl concentration as described by each protocol. Using a simulation allowed identical doses of the drug to be administered and compared. When we superimposed the disposition curve predicted by our pharmacokinetic parameters on the simulated concentrations from McClain's study (fig. 7), our parameters predicted the simulated concentrations from McClain's study quite well. Although our parameters predicted larger initial concentrations, there were only two samples in the first 5 min so this error contributed little to the overall performance.

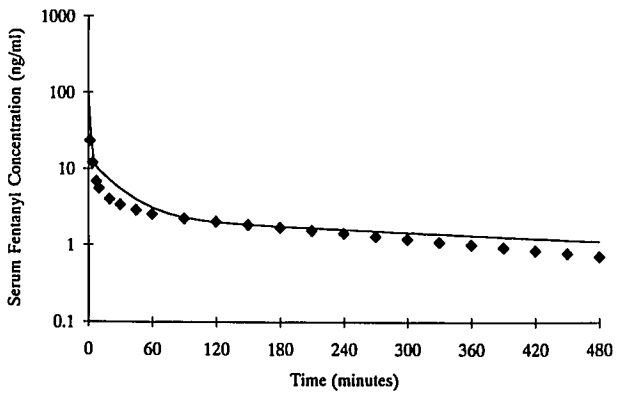

FIG. 7. Simulated fentanyl concentrations from McClain and Hug's study[8] (diamonds) superimposed on the disposition predicted by the pharmacokinetic parameters from the current study (line). At the times sampled in McClain and Hug's study, the disposition curve from our pharmacokinetics predicted McClain and Hug's observations.

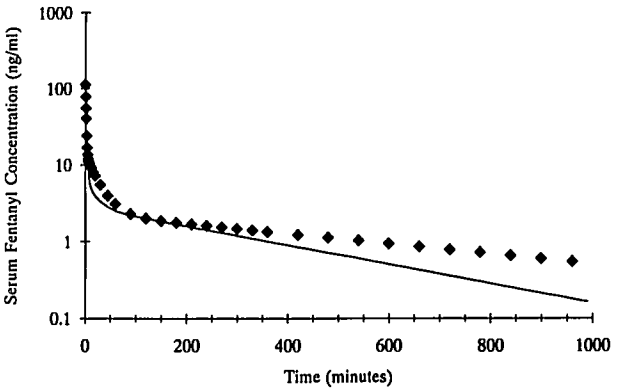

FIG. 8. Simulated fentanyl concentrations from the current study (diamonds) superimposed on the disposition predicted by the pharmacokinetic parameters reported by McClain and Hug[8] (line). The disposition curve underpredicts the initial concentrations and the concentrations after 400 min.

When we superimposed the disposition curve predicted by McClain's pharmacokinetic parameters on the simulated concentrations from our study (fig. 8), the simulated concentrations from our study and those predicted by McClain's pharmacokinetics diverged after 400 min, producing large performance errors. Large performance errors are also seen in the first few minutes following the bolus when we sampled intensively. Thus, the relatively poor predictive performance of McClain's pharmacokinetics resulted from the large errors seen in the first few minutes and after 400 min.

In Scott's, Hudson's, and Varvel's studies, the serum fentanyl concentrations were measured for nearly 24 h. The relative inability of McClain's parameters to predict Scott's, Hudson's, and Varvel's observations was due primarily to the prediction of a more rapid decay in fentanyl concentration than was observed. McClain's fentanyl study was conducted in volunteers, which limited the amount of fentanyl that could be ethically administered. Samples were drawn until the concentration fell below the limits of detection of the assay. This occurred at 8 h and resulted in estimation of a more rapid terminal half-life than was observed in subsequent patient studies.

Alvis *et al.* reported good performance with the CACI device when the pharmacokinetic parameters of McClain were used.[4,5] Our results do not contradict the results of Alvis *et al.* As can be seen in figure 7, at the times sampled by McClain, there is fairly good agreement between the predictions of our pharmacokinetic parameters and the simulated concentrations from McClain's study. Alvis *et al.* did not draw frequent blood samples after each change in C_P nor did they continue to sample after the conclusion of the operation; thus, they did not draw samples at the

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times that contributed most strongly to the relatively worse performance of McClain's parameters in our study.

Our study highlights an important principle when designing dosing regimens based upon pharmacokinetic research: it is usually reasonable to interpolate between the times sampled in the original research, but it is almost never reasonable to extrapolate beyond the time period analyzed. We drew samples both earlier and later than in McClain's study; therefore, it was not, *a priori,* reasonable to expect pharmacokinetics from that study to predict our observations. This also applies to others who might dose their patients using our pharmacokinetics parameters: arterial concentrations before 1 min (if any) or beyond 10 h may not be well predicted.

In summary, we have described the performance of a CCIP administering fentanyl according to two published pharmacokinetic parameter sets. We derived new pharmacokinetics from these data and demonstrated that our derived pharmacokinetic parameters not only predict our fentanyl concentration *versus* time data but also predict the fentanyl concentration *versus* time data from previous studies. Finally, we demonstrated that infusion regimens designed from pharmacokinetic studies may not perform well during time periods not sampled in the original research.

Appendix

The analysis in part 3 of how well each of the 11 parameter sets predicted each of the five data sets is an analysis of the residual variability given a certain *likelihood* that the parameter set describes the mean parameters for the population. For normally distributed performance errors ($C_M - C_P$), the likelihood, L, is defined as:

$$L = \prod_{i=1}^{n} \frac{1}{\sigma_i\sqrt{2\pi}} e^{-\frac{1}{2\sigma_i^2}(C_{M_i} - C_{P_i})^2}$$

where σ_i is the SD of C_{M_i} and n is the number of samples in the population. When the magnitude of the errors are proportional to the predicted observations (C_P), we can define a variance scale parameter, σ, such that $\sigma_i = \sigma C_{P_i}$. Substituting this model for variance into the likelihood calculation and rearranging the exponent produces:

$$L = \prod_{i=1}^{n} \frac{1}{\sigma C_{P_i}\sqrt{2\pi}} e^{-\frac{1}{2\sigma^2}\left(\frac{C_{M_i} - C_{P_i}}{C_{P_i}}\right)^2}$$

Given the definition of PE_i, the above equation can be simplified to:

$$L = \prod_{i=1}^{n} \frac{1}{\sigma C_{P_i}\sqrt{2\pi}} e^{-\frac{1}{2\sigma^2} PE_i^2}$$

Taking the log of both sides yields the log likelihood:

$$\log (L) = n \log\left(\frac{1}{\sqrt{2\pi}}\right) - \sum_{i=1}^{n}\left(\log (\sigma C_{P_i}) + \frac{1}{2\sigma^2} PE_i^2\right)$$

MK-MODEL maximizes log likelihood using extended least squares nonlinear regression. To find the value of σ that maximizes the log likelihood, we can differentiate this expression with respect to σ and set the result to 0:

$$0 = \sum_{i=1}^{n}\left(-\frac{C_{P_i}}{\sigma C_{P_i}} - \frac{1}{2}\frac{(-2)}{\sigma^3} PE_i^2\right)$$

The above equation simplifies to:

$$0 = -n\sigma^2 + \sum_{i=1}^{n} PE_i^2$$

Solving for σ yields:

$$\sigma = \sqrt{\frac{\sum_{i=1}^{n} PE_i^2}{n}} = \text{RMS error}$$

where n is the number of samples in the entire study population.

Thus, the RMS error is the maximum likelihood (extended least squares) estimator for σ. Since σ is the underlying residual variability and the RMS error is the maximum likelihood estimator for σ, then the RMS error is a statistically valid measure of the residual variability between the predictions of the pharmacokinetic models and the observations.

As noted by Peck *et al.*, minimizing iteratively reweighted least squares (and thus RMS error) is very nearly equivalent to maximizing likelihood when the errors are relatively small.[20]

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