Anesthesiology
78:260–265, 1993

J. B. Lippincott Company, Philadelphia

Sufentanil Disposition

Is It Affected by Erythromycin Administration?

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Background: **Because oral erythromycin administration has been associated with reduced elimination of alfentanil, suspicion has been raised about related opioids with similar metabolic pathways. A controlled crossover study of sufentanil pharmacokinetics was undertaken to resolve this issue.**

Methods: **Six subjects had measurements of plasma concentrations for 9 h after intravenous administration of sufentanil (3 μg/kg). Each subject was studied following no erythromycin (control) and after 1- and 7-day courses of erythromycin base.**

Results: **Plasma concentrations during the 9 h of measurement were similar before and after erythromycin. Terminal half-life and clearance and distribution volume did not change significantly among treatment groups. Values measured after 7 days of erythromycin were similar to controls.**

Conclusions: **Prior administration of erythromycin does not alter pharmacokinetics of sufentanil in the 9 h following sufentanil administration. Thus, there are no apparent clinical consequences of prior or concomitant erythromycin administration in patients receiving sufentanil for procedures of 9 h or less. (Key words: Anesthesia, intravenous: sufentanil. Interactions, drug: erythromycin-sufentanil. Pharmacokinetics.)**

SUFENTANIL is a potent opioid used regularly in anesthetic practice. Its unique characteristics are high potency, high lipid solubility, and a relatively brief duration of action under most circumstances. This allows a rapid and predictable recovery from its anesthetic effects.[1,2] Recently, the metabolism of alfentanil has been found to be impaired when it is given after a course of erythromycin.[3] Prolonged sedation and severe respiratory depression have been reported[4] as a result. A reduction of sufentanil clearance by erythromycin could lead to similar effects. To determine whether this interaction is significant, a controlled crossover study of sufentanil pharmacokinetics was undertaken. Several preparations including erythromycin base, estolate, ethylsuccinate, and stearate have been shown to inhibit the metabolism of theophylline,[5] the best studied erythromycin interaction. This inhibition was demonstrable after a 4–7-day course of erythromycin but not after a single dose.[6] This is similar to the results found for alfentanil.[3] We therefore proposed to determine whether erythromycin base given for either one dose or 7 days would alter the disposition of sufentanil and lead to elevated plasma concentrations.

Methods and Materials

Six male subjects aged 25–45 who had previously participated in a similar study of erythromycin's effect on alfentanil pharmacokinetics[3] gave written informed consent to participate in this Institutional Review Board-approved study. All were found to be in normal health by medical history and physical examination and were within 10% of ideal body weight. One subject had a history of smoking; no subject had a history of drug use. All refrained from alcoholic beverages for 7 days before their study dates and took no food after midnight on the day of study. The subjects were given sufentanil on three separate occasions: once after no medication (control dose); once after a single 500-mg oral tablet of erythromycin (E-Mycin) given 90 min before sufentanil; and once after a 7-day course of 500 mg erythromycin twice a day. A crossover design was implemented so that all six possible orders of erythromycin administration were employed. At least 2 weeks elapsed between studies in the same subject.

Studies were begun at 6:30 AM with oral administration of 50 mg naltrexone to block the sedative and respiratory depressant effect of sufentanil. This was followed by placement of a venous catheter for blood

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Received from the Department of Anesthesiology, Thomas Jefferson University, Philadelphia, Pennsylvania. Accepted for publication October 14, 1992. Supported in part by a grant from Janssen Pharmaceutic.

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sampling and a second venous catheter in the opposite arm for drug administration. Naloxone (0.4 mg) was given intravenously and an additional 0.4 mg was mixed with the sufentanil to augment the receptor block during the initial peak concentrations. Sufentanil (3.0 μg/kg) was administered as an infusion for 5 min into a venous catheter, followed by a total of 500 ml 0.9% NaCl solution administered over the next 25 min.

Ten-milliliter blood samples were drawn and placed on ice for subsequent serum separation. Samples were collected prior to and 6, 10, 15, 30, 60, 120, 180, 240, 300, 360, 420, 480, and 540 min after the start of the infusion. Serum samples were kept at −20° C until analyzed. For the first hour after sufentanil administration, heart rate and blood pressure were monitored by an automated blood pressure device (Dinamap®, Criticon, Tampa, FL). Respiratory rate was measured by an observer.

Samples were measured in duplicate for sufentanil by a radioimmunoassay method.[7] This radioimmunoassay uses rabbit antibodies and has a sensitivity of 0.06 ng/ml, and inter- and intra-assay coefficients of variation were 9.7% over the range from 0.1 to 4 μg/ml. No cross reactivity was found between the assay and either metabolites or related opiates. The individual concentration-time curves were fit to sums of two and three exponentials using nonlinear least squares regression (Nonlin SYSTAT). The weighting factor was

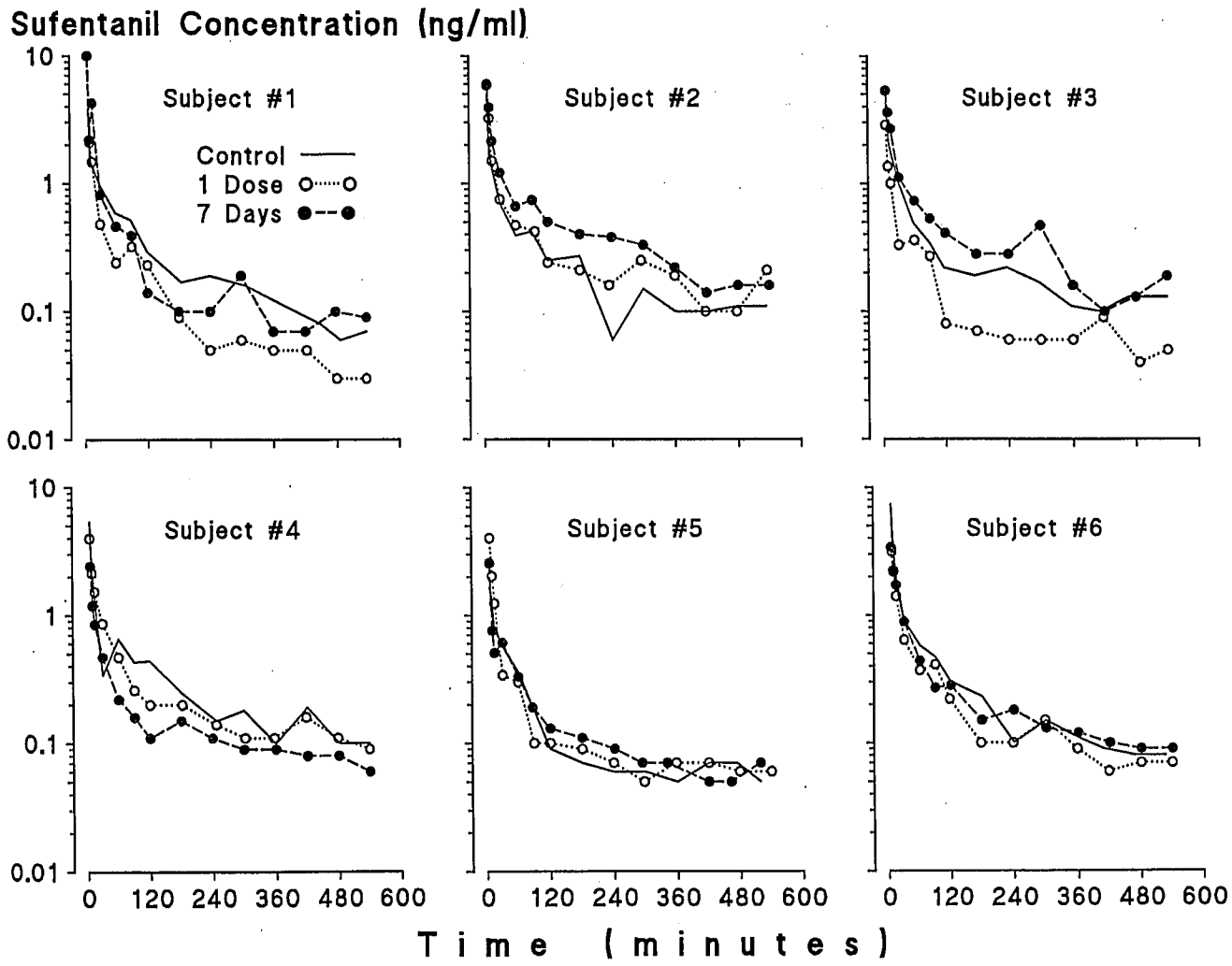

Fig. 1. Plasma sufentanil concentration for the six subjects. Control values and those after one dose and 7 days of erythromycin are shown.

set to (predicted concentration)$^{-2}$. The addition of a third exponential to the pharmacokinetic model was determined by analysis of variance as described by Boxembaum *et al.*[8] When the additional term improved the fit ($P < .05$) the three-exponential model was chosen; otherwise, a two-exponential model was used.

The constants of the exponential terms were corrected for the 5-min infusion by the method of Loo and Riegelman.[9] Derived parameters (clearance and distribution volume [Vd_{ss}]) were calculated according to standard methods[10] for bolus administration and normalized to the actual subject weight.

Statistical analysis of the kinetic parameters was performed using analysis of variance for repeated measures.[11] Plasma concentrations also were compared by the same test. Sufentanil concentrations for each subject and all three erythromycin treatments from the period 90–540 min were analyzed in this fashion. Where a significant F value was found, the least significant difference test was used for comparisons between means. In all cases $P < .05$ was required to claim statistical significance.

Results

For all studies, control plasma sufentanil concentrations (prior to sufentanil administration), both before and after naloxone, were undetectable. After the initial maximum at 6 min, there was a rapid decrease in plasma sufentanil concentration. The plasma concentration of sufentanil for each subject is shown in figure 1. Three curves are depicted for each subject representing the three separate measurements: control, 1 day, and 7 days of erythromycin pretreatment. The plasma concentrations of sufentanil over the period from 90 to 540 min were not different ($P > .4$) among the controls and two erythromycin treatments. The statistical test had the power to detect a 34% difference in the plasma drug concentration between groups. Actual differences as seen in figure 1 are much less; the average difference from control to 7 days of treatment was 15%. Analysis of the pharmacokinetic parameters in individual subjects is presented in table 1. A three-exponential fit was preferred for five of the data sets, subject 1 at control, subject 4 at 7 days, subject 5 at 7 days, and subject 6 at control and 7 days. For all others, a two-exponential fit was adequate and used for pharmacokinetic analysis. None of the parameters (terminal half-life, Vd_{ss}, or clearance) showed a significant difference ($P > .4$) for an effect of erythromycin.

Subjective effects were noted in all subjects during sufentanil administration. A feeling of warmth throughout the body along with a sensation described as "dizziness" or "lightheadedness" was almost always described during the 5-min drug infusion. No major changes were noted in the subject's heart rate, blood pressure, or respiratory rate. Throughout the study period, nausea was a frequent occurrence, especially during the first 2–3 h after sufentanil administration. This was severe enough to lead to treatment with 5 mg intravenous prochlorperazine in 9 of the 18 investigations. This was noted in five of the six subjects and occurred without regard to erythromycin pretreatment.

Discussion

Whereas the clearance of alfentanil was shown to be significantly reduced in a similar study on the same subjects,[3] sufentanil clearance was not significantly affected. To see the magnitude of an erythromycin effect that can lead to clinical consequences, figure 2 shows concentration data of alfentanil from a previous study[3]

Table 1. Pharmacokinetic Parameters Related to Sufentanil Disposition for the Six Subjects Measured after No Dose, One Dose, or 7 Days of Erythromycin

Subject No.	Age (yr)	Weight (kg)	Terminal Half-life (min)			Vd_{ss}			Clearance (ml · kg^{-1} · min^{-1})		
			0 Days	1 Day	7 Days	0 Days	1 Day	7 Days	0 Days	1 Day	7 Days
1	35	78	204	129	212	0.85	1.30	1.87	8.4	16.1	11.8
2	45	93	225	362	204	3.93	4.39	2.29	15.7	10.7	9.6
3	32	70	368	182	257	4.96	5.52	2.79	13.2	27.2	9.5
4	29	77	201	406	384	3.37	5.96	9.06	14.4	14.6	23.3
5	31	73	486	704	728	11.13	10.87	12.79	25.3	17.6	18.6
6	27	68	358	184	323	3.45	3.95	5.12	13.2	20.0	16.2
Mean	33.2	76.5	307	328	351	4.62	5.33	5.65	15.0	17.7	14.8
SD	64	9.0	116	215	197	3.47	3.17	4.40	5.6	5.6	5.5

for two subjects who were sensitive to erythromycin's effect. These are the same subjects as 1 and 2 of this study. The design of that study was similar to the present. Overall it showed a significant reduction of alfentanil clearance after 7 days of erythromycin treatment. This led to the slower decrease in blood concentration shown in figure 2. Higher drug concentrations after erythromycin pretreatment are visible for alfentanil; the concentrations after 7 days of treatment are 18 and 10 times greater than controls at the end of 6 h. On the other hand, sufentanil concentrations for all treatments in the present study overlap over the 9-h measurement period. The results for the two drugs are different despite their similar structure. This could explain the report of prolonged sedation and respiratory depression following normal amounts of alfentanil in patients receiving erythromycin, whereas no such problem has been reported with sufentanil.

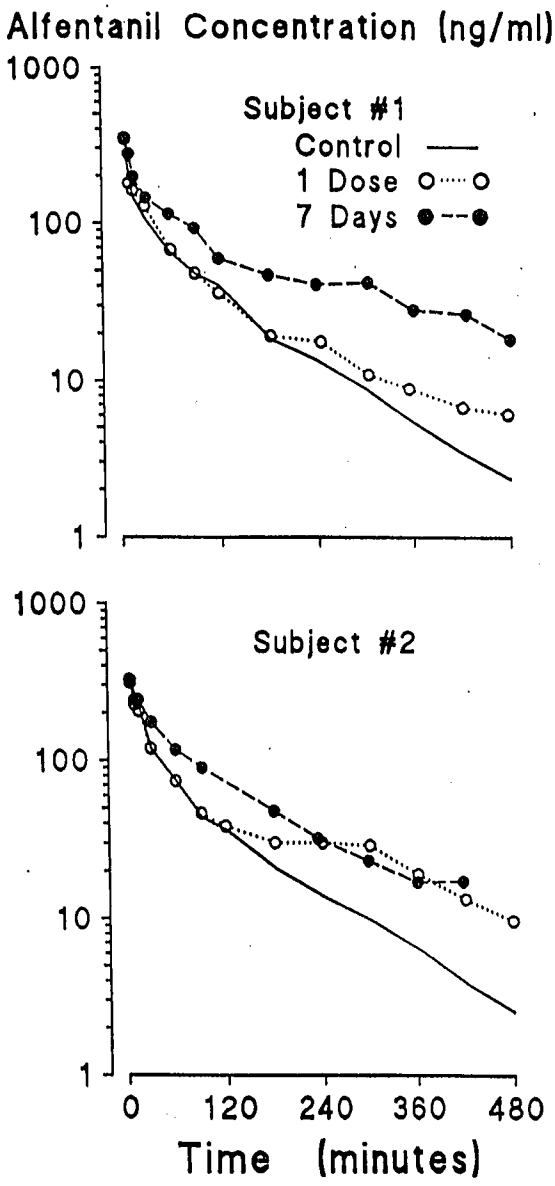

Fig. 2. Data from an earlier study describing plasma alfentanil concentration for 6 h after 50 μg/kg for two subjects sensitive to erythromycin's effects.[3] Control values and those after one dose and 7 days of erythromycin are shown. Subjects are the same as no. 1 and 2 of this study.

Known metabolic pathways for sufentanil elimination strongly resemble those of alfentanil.[12] For both drugs, the major Phase I pathway is oxidative-N-dealkylation at the common piperidine nitrogen.[12,13] This is the point at which it has been suggested[6] that the erythromycin effect is exerted (*i.e.*, by competitive inhibition of N-demethylation by erythromycin).[14,15] Recent measurements on human microsomes demonstrate that the oxidative degradation of alfentanil and sufentanil are inhibited (50%) by very similar concentrations of propofol.[16] This strongly suggests that the same isoenyzme is responsible. If this process is the rate-limiting step for sufentanil as it is for alfentanil, then sufentanil elimination should be reduced by erythromycin administration. There are a number of explanations as to why this was not seen in the current study.

First, sufentanil metabolism may be different from that of alfentanil. However, as stated above, this does not appear to be the case. Second, the subjects involved are unusual and did not show the effect. The same subjects, however, were sensitive to erythromycin inhibition of alfentanil elimination since the subjects of the present study were the same individuals as the previous study. In fact, subjects 1 and 2 were very sensitive to this regimen of erythromycin. Even in these subjects, no erythromycin-sufentanil interaction was noted.

A more likely explanation might be a result of pharmacokinetic differences between sufentanil and alfentanil. Superficially, the differences between alfentanil and sufentanil do not appear to be great. The pharmacokinetic study of Bovill *et al.*[1] found a half-life of 164 min for sufentanil, similar to that of alfentanil (84 min).[3] Sufentanil, however, is much more lipid-soluble than is alfentanil. This fact was brought out in a more detailed investigation of sufentanil pharmacokinetics by Hudson *et al.*[17] They used repeated doses and a larger total dose of sufentanil to follow its disposition for a longer time (24 h *vs.* 8 h). This resulted in a different set of phar-

macokinetic parameters than those reported by Bovill *et al.* These are compared in table 2. The new parameters give sufentanil a much larger distribution volume and longer terminal half-life than had been estimated previously. The parameters of the present study are intermediate between those of Bovill *et al.* and Hudson *et al.* The more recent parameters are consistent with sufentanil's high lipid solubility.

It is worthwhile to compare the disposition data of Bovill *et al.* with those of Hudson *et al.* Figure 3 shows the plasma sufentanil concentrations obtained from Bovill *et al.*'s and Hudson *et al.*'s pharmacokinetic parameters after adjusting their disposition function to the dose given in this study. Average data from this study are shown for comparison. The similarities between the curves are remarkable considering the wide disparity of the parameters in table 2. Differences appear to be within the scatter of the data down to the limits of detectability (0.06 ng/ml). Note that the control (no erythromycin pretreatment) data points from this study are close to both curves. Thus the parameters derived by both Hudson *et al.* and Bovill *et al.* describe the range of typical concentrations over the first 9 h. This can explain the results of the current study. Over the 9 h of the study, the estimate for clearance probably is due to a summation of two factors, metabolic clearance and a component of intercompartmental (or distributional) clearance. Therefore, the estimate we obtained likely represents a slight overestimate of the true metabolic clearance of sufentanil.

This explanation leads to several important conclusions about sufentanil that are consistent with all of the data. First, its disposition over a typical time span (less than 9 h) will be unaffected by erythromycin administration since its clearance over this interval represents redistribution to a deep compartment. Very long-term administration (longer than the 9 h of this study) and total dose greater than 3 μg/kg may lead to a more prolonged recovery. At this higher dose range, erythromycin may prolong recovery further, but at present any erythromycin effect is undocumented.

Table 2. Comparison of Sufentanil Pharmacokinetic Parameters Derived by Bovill *et al.*[1] *Versus* Those of Hudson *et al.*[16]

	Bovill *et al.*	Hudson *et al.*
Vd_{ss} (L/kg)	1.74 ± 0.60	8.7 ± 4.5
Terminal half-life (min)	164 ± 69	726 ± 348
Clearance ($ml \cdot kg^{-1} \cdot min^{-1}$)	12.7 ± 2.5	15 ± 3

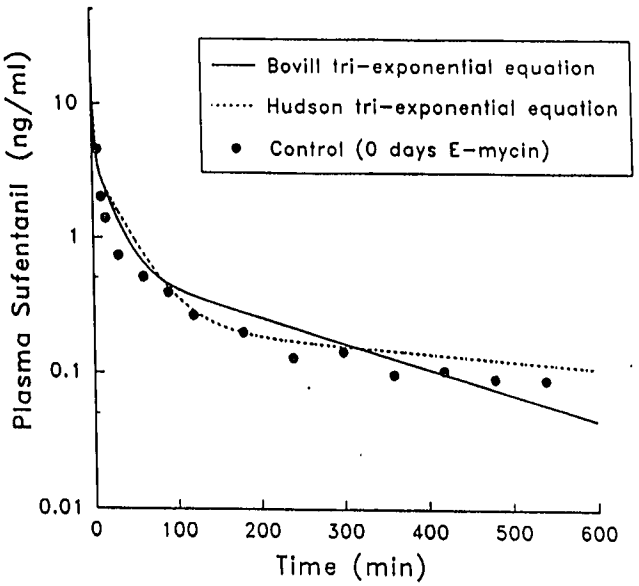

Fig. 3. Pharmacokinetic disposition function for a 3-μg/kg dose based on the parameters of Bovill and those of Hudson compared. For reference, the average control (no erythromycin) values from this study are presented also.

In conclusion, there is no significant effect on sufentanil disposition by prior administration of up to 7 days of oral erythromycin, when moderate doses of sufentanil are administered. Sufentanil disposition in practice is dominated by its redistribution to a large volume. Sufentanil in doses of 3 μg/kg or less can be recommended, therefore, for procedures of normal length, even in patients who have received erythromycin. Much larger doses of sufentanil, whether administered for shorter or longer periods, should be administered with caution because of the likelihood of prolonged recovery. Administration of sufentanil in this manner requires further study.

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