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Comparative Tissue Concentration Profiles of Fentanyl and Alfentanil in Humans Predicted from Tissue/Blood Partition Data Obtained in Rats

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The steady-state tissue/blood partition coefficients of fentanyl and alfentanil were determined in 13 organs and tissues in the rat. A 6-h infusion of both drugs was used in order to achieve steady-state. Blood and tissue concentrations of drugs were measured by gas-liquid chromatography. The partition coefficients of fentanyl were two- to 30-fold higher than those of alfentanil. These data were then used in a physiologic pharmacokinetic model describing the disposition of the two opioids in humans. The model predicted the plasma pharmacokinetics of these drugs in humans reasonably well. However, simulation beyond 24 h after a bolus administration showed a terminal half-life of 20 h for fentanyl, *i.e.*, an elimination phase that has not yet been described in actual pharmacokinetic studies. In keeping with this, the volume of distribution of fentanyl in the model was also larger than expected. The simulated tissue concentration curves of fentanyl and alfentanil in humans could be used to explain the propensity of fentanyl to give secondary peaks in plasma concentration curves and the difference in effect kinetics between the two opioids. Physiologic pharmacokinetic modeling, based on measured data in small animals, can generate information that is not obtainable by empirical methods in humans. (Key words: Analgesics: alfentanil; fentanyl. Pharmacokinetics: distribution; kinetics; models; uptake. Solubility: partition coefficients.)

FENTANYL AND ALFENTANIL are synthetic opioids with similar effects but different pharmacokinetics.[1] Compared with fentanyl, alfentanil is less lipophilic, has a smaller volume of distribution, a lower clearance, and a shorter terminal half-life. After bolus doses, the effects of both drugs are terminated by redistribution from the CNS to peripheral tissues. The plasma pharmacokinetics of fentanyl and alfentanil in humans are reasonably well known. The plasma pharmacokinetics do not, however, explain why alfentanil has a more rapid onset and dissipation of effect than fentanyl,[2] nor the lack of parallelism between recovery in the EEG and the decrease in fentanyl or alfentanil concentrations in plasma.[3] Nor have standard pharmacokinetic investigations been able to explain the common occurrence of a secondary peak in the plasma concentration curve of fentanyl.[1] Determination of drug concentration profiles in tissues allows the study of the redistribution of drug between tissues and may address these unresolved issues. For obvious reasons, tissue concentration curves can not be obtained in humans by ordinary empirical methods of sampling and assay. They can, however, be computer simulated from knowledge of three characteristics for each tissue or organ: the steady-state tissue/blood partition coefficient, the tissue (or organ) volume, and the regional blood flow. Also, the total body clearance and the dose of the drug must be known.

We have therefore measured the steady-state tissue/blood partition coefficients of fentanyl and alfentanil in 13 tissues in the rat. We have then used these data in a physiologic pharmacokinetic model to simulate the drug concentration profiles in those organs and tissues in humans that govern the pharmacokinetics of the drugs and the time courses of drug effects. These concentration profiles were then used to describe the differences between fentanyl and alfentanil as regards uptake into the brain, potential for "renarcotization" by release of drug from tissue depots, and rate of elimination from the body.

Methods

Drug Infusions in Conscious Rats

Approval of the research protocol was obtained from the Stanford Administrative Panel for Laboratory Animal Care. In order to minimize interindividual differences, we measured the partition coefficients in animals given simultaneous infusions of fentanyl and alfentanil. However, to verify that the tissue partitioning was not influenced by a pharmacokinetic interaction between the two drugs, measurements were also made in animals that received fentanyl or alfentanil alone.

Male F1 hybrid rats (F334 × Brown Norway, Charles Rivers Breeding Laboratories, Kingston, NY) were anesthetized with isoflurane, and Teflon® catheters were inserted into a jugular vein and into the aorta by way of a tail artery. The catheters were exteriorized at the neck

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and the animals were allowed to recover over one or two nights before the experiment. A saline solution of fentanyl citrate, alfentanil hydrochloride, or both was infused over 6 h by a syringe pump (Harvard Instruments, Boston, MA) *via* the venous catheter. The infusion rates were 13 $\mu g \cdot kg^{-1} \cdot h^{-1}$ for fentanyl and 120 $\mu g \cdot kg^{-1} \cdot h^{-1}$ for alfentanil.¶ Throughout the experiment, the rats were spontaneously breathing room air.

Of the 16 animals used, three (374–399 g) that received fentanyl alone, three (380–395 g) that received alfentanil alone, and five (362–439 g) that received the combination were included in the data analysis, while the remaining five were excluded because of diverse technical failures. Blood gas data from one of the excluded five was used. Blood samples were obtained from the arterial catheters, which were intermittently connected to a pressure transducer that gave recordings of heart rate and blood pressure on a Grass polygraph recorder (Grass Instruments, Quincy, MA). Samples (80 μl) for analysis of blood gases were collected hourly and samples (0.5 ml) for drug analysis were collected at 4, 5, and 6 h only. One milliliter of arterial blood was withdrawn into a heparinized syringe, the sample to be analyzed was then collected by spontaneous outflow from the catheter, and the drawn blood was reinjected followed by 1 ml of heparin/saline. This sampling technique limited the blood loss to less than 3 ml over the 6 h. At the end of the experiment, the infusion was stopped, the contents of the venous catheter were aspirated, and the rat was decapitated within half a minute. The blood was collected in a beaker rinsed with heparin and part of it was centrifuged to give a plasma sample. The rat was dissected and organs and tissues were collected as enumerated in table 1. The stomach contents were also collected. All organ and tissue samples were wrapped in aluminium foil and frozen on dry ice. To prevent desiccation of the tissues, the foil packages were placed in 5.5 × 9 cm plastic zip-lock bags that were then collected in larger bags. The samples were kept at −20° C until assay within 2 weeks.

Drug Assay

The organs were weighed and all samples were assayed by capillary column gas chromatography with nitrogen-selective detection.[4] This procedure allows the independent quantitation of fentanyl and alfentanil in the same sample down to tissue concentrations of 0.5–1 ng/g. The coefficient of variation (CV) of the assay is typically 2–9% at tissue concentrations of 0.8–32 ng/g.

Data Analysis and Computer Simulations

The total body clearance of fentanyl and alfentanil was calculated by the following formula: clearance (CL) equals infusion rate divided by steady-state blood concentration. The tissue/blood partition coefficients were calculated by division of the tissue drug concentrations with the drug concentration in the 6-h blood sample. For liver, a correction for clearance was made.[5]

The blood/plasma partition coefficients were calculated as the drug concentration in blood divided by the drug concentration in plasma in the decapitation samples. Blood clearance was converted to plasma clearance by multiplication by the blood/plasma partition coefficient.

An 11-compartment physiologic model (fig. 1) was used to simulate the time courses of drug concentration in blood and tissues in a 70-kg human. The model takes into consideration the drug tissue/blood partition coefficients (R), which were assumed to be the same in humans as in the rat, the blood flows to the tissues (Q), and the volumes of each tissue (V) in humans. The specific equations used are given in the appendix. Stomach, small intestine, and large intestine were lumped into one compartment, and spleen and pancreas into another. The testes (which in rats are bigger than the kidneys) were not included in the model.

The mean transit times (MTT) and mean residence times (MRT) of the drugs in the tissue compartments were defined and calculated according to Covell *et al.*[6]

Student's *t* test was used to compare mean values and $P < 0.05$ was considered as significant.

TABLE 1. Steady-State Tissue/Blood Partition Coefficients (R) of the Opioids in Rats

Organ/tissue	Fentanyl (R_F)	Alfentanil (R_A)	R_F/R_A
Brain	4 ± 0.66	0.18 ± 0.08	22.2
Heart	5.1 ± 0.62	0.79 ± 0.27	6.5
Lungs	15.3 ± 2.50	1.11 ± 0.27	13.8
Stomach	14 ± 2.59	7.49 ± 2.21	1.9
Small intestine	9 ± 1.24	0.95 ± 0.25	9.5
Large intestine	5.4 ± 2.85	0.64 ± 0.16	8.4
Liver	4.3 ± 1.06	1.43 ± 0.18	3
Pancreas	24.1 ± 3.26	1.37 ± 0.22	17.6
Spleen	31.3 ± 5.28	1.05 ± 0.22	29.8
Kidneys	13.7 ± 2.18	1.18 ± 0.36	11.6
Testes	9.2 ± 1.62	0.48 ± 0.12	19.2
Muscle	3.5 ± 1	0.44 ± 0.10	8
Fat	30.2 ± 5.98	3.01 ± 0.41	10

Mean ± S.D., n = 8 for each tissue.
Each sample can be converted to tissue/plasma partition coefficients by multiplication with the blood/plasma partition coefficients; 0.892 for fentanyl and 0.699 for alfentanil.

Results

Measured Data in the Rats

The blood concentrations of fentanyl and alfentanil reached during the infusions are shown in figure 2. The effects of the simultaneous infusion of the two drugs on

¶ Doses and drug concentrations are given as for free base.

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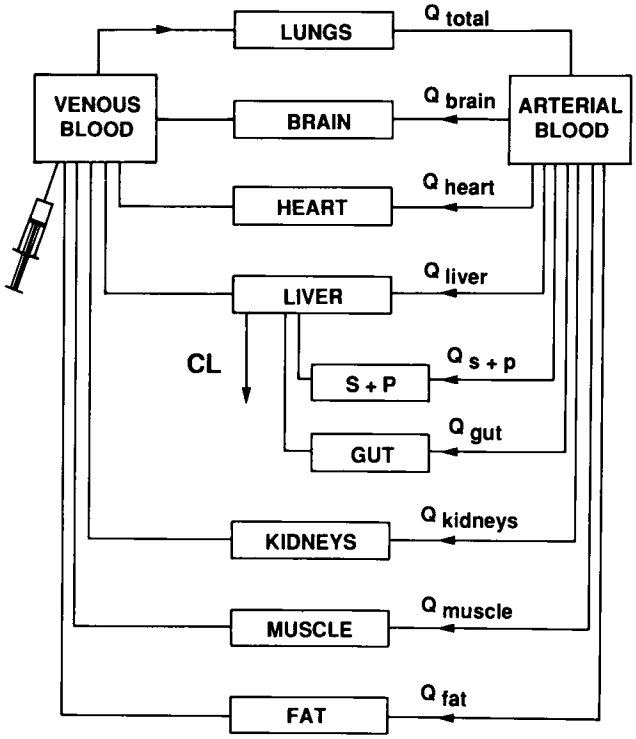

FIG. 1. The structure of the physiologic model used to simulate the tissue concentration curves of fentanyl and alfentanil in humans. "Gut" denotes stomach, small intestine, and large intestine. "S + P" denotes spleen and pancreas.

arterial blood gases are also depicted. At the beginning of the infusion, the rats assumed a crouched, rigid position but continued to breathe spontaneously. Toward the end of the infusion they started to move about, eat, and drink.

The steady-state blood concentrations of fentanyl were 3.5 ± 0.07 ng/ml (mean ± SD) in the three rats that received this drug alone and 3.2 ± 0.40 ng/ml in the five rats that received fentanyl and alfentanil together. The corresponding mean blood clearance in all eight rats was 67 ± 8.8 ml·min^{-1}·kg^{-1}, which is approximately equal to the reported total liver blood flow in rats.[5] For alfentanil, the steady-state blood concentrations were 41 ± 9.6 ng/ml in the three single-drug animals and 50 ± 8.8 ng/ml in the five rats that received the combination. The mean blood clearance was 45 ± 8.5 ml·min^{-1}·kg^{-1}. The blood/plasma partition coefficient was 0.892 ± 0.049 for fentanyl and 0.699 ± 0.077 for alfentanil. Consequently, the mean plasma clearance values were 60 ± 7.8 ml·min^{-1}·kg^{-1} for fentanyl and 31 ± 5.9 ml·min^{-1}·kg^{-1} for alfentanil.

Table 1 provides the calculated tissue/blood partition coefficients of fentanyl and alfentanil in rat tissues. The partition coefficients shown are the means from all animals. When we divided the mean partition coefficients of all rats into the mean partition coefficients from rats receiving a single drug and from rats receiving the combination, there were only small differences between the data sets (means differing by less than 16% for fentanyl and less than 25% for alfentanil). The one exception was liver, where the mean partition coefficient for fentanyl was 3.07 in the animals treated with this drug alone and 4.67 in the animals treated with the combination ($P < 0.01$). Of the total infused doses, 1.8 ± 0.33% of the fentanyl and 2.6 ± 0.83% of the alfentanil was found in the stomach contents.

Computer Simulations in Humans

Table 2 shows the calculated apparent volumes of distribution of fentanyl and alfentanil in various organs and tissues for a 70-kg human as well as the calculated mean transit times (MTT) and mean residence times (MRT) of the opioids in these organs and tissues. The sums of the apparent volumes of distribution are 540 l for fentanyl

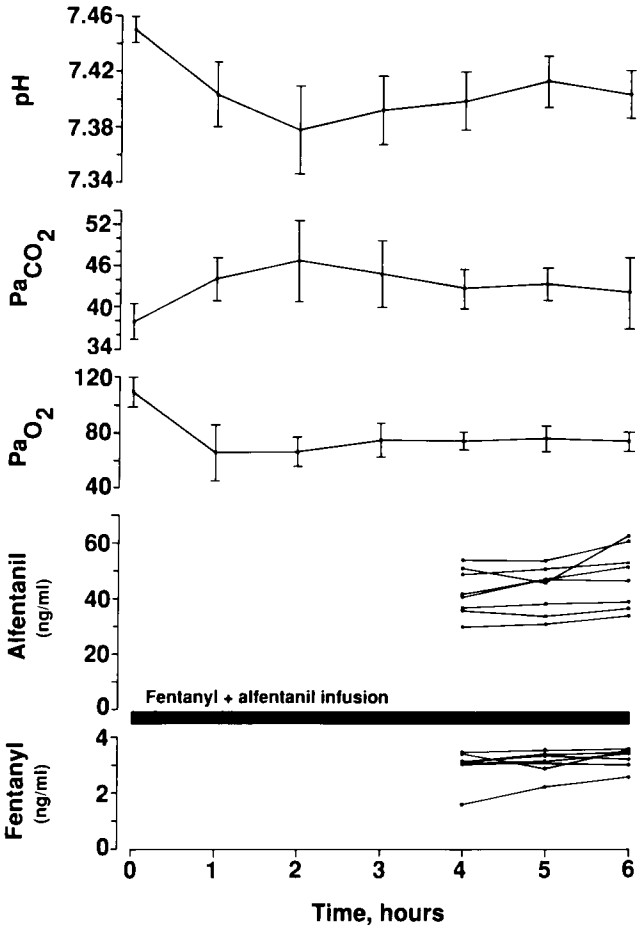

FIG. 2. Measured blood concentrations of fentanyl and alfentanil during the infusions in the rats. Above are the pooled blood gas values from six rats given the combined infusion of fentanyl and alfentanil. The error bars depict standard deviations. The difference in pH between 2 and 5 h is significant ($P < 0.05$).

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TABLE 2. Physiologic Data and Pharmacokinetic Parameters of the Organs and Tissues in the Model for a 70-kg human

Organ/tissue	Q (ml/min)	V (l)	Fentanyl V_{app} (l)	Fentanyl MTT (min)	Fentanyl MRT (min)	Alfentanil V_{app} (l)	Alfentanil MTT (min)	Alfentanil MRT (min)
Brain	760	1.5	6	7.9	7.5	0.27	0.36	0.49
Heart	240	0.3	1.5	6.4	1.9	0.24	1	0.43
Lungs	6300	1.2	18.4	2.9	23	1.33	0.21	2.41
Gut*	700	2.4	17.3	24.7	21.6	1.91	2.73	3.47
Liver (total)	1600	1.5	6.5	3	6.1	2.15	1.34	3.20
Pancreas	500	0.09	2.2	17	10	0.12	0.66	0.64
Spleen		0.2	6.3			0.21		
Kidneys	1200	0.3	4.1	3.4	5.2	0.35	0.29	0.64
Muscle	300	30	105	350	130	13.2	44	24.1
Fat	260	12.2	368	1418	461	36.7	141.2	66.8
Blood†	—	5.4	5.4	1.2	6.8	5.40	1.20	9.80

The physiologic data (compiled from references 5 and 7) are Q = blood flow and V = actual volume of the organ/tissue.

The pharmacokinetic parameters are V_{app} = apparent volume of the tissue compartment (*i.e.*, V · R), MTT = mean transit time, and MRT = mean residence time of the drug in the tissue.

* Stomach, small and large intestine. R was set equal to the mean of R (small intestine) and R (large intestine). See Discussion.

† Arterial plus venous blood.

and 61.9 l for alfentanil. Note that these volumes assume blood as the sampling site. As explained in the discussion, the total volume of distribution of alfentanil becomes 39.0 l for tissue/plasma partitioning.

Figures 3 A and B show the computer-simulated bolus dose pharmacokinetics of fentanyl and alfentanil in humans. Lungs, brain, heart, and kidneys are compartments where the ratio of apparent volume to blood flow is low,

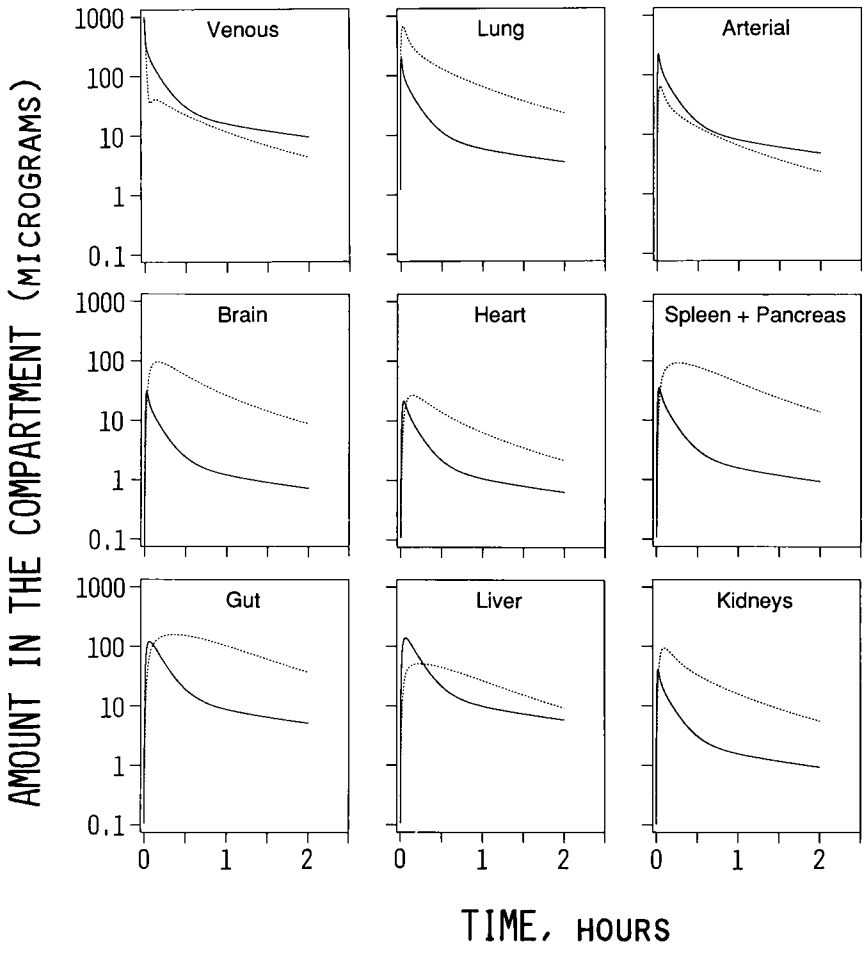

FIG. 3. *A* Computer simulations of the amounts of fentanyl (*dashed curves*) or alfentanil (*continuous curves*) in various organs and tissues in a 70-kg human after a bolus iv injection of 1 mg of either drug.

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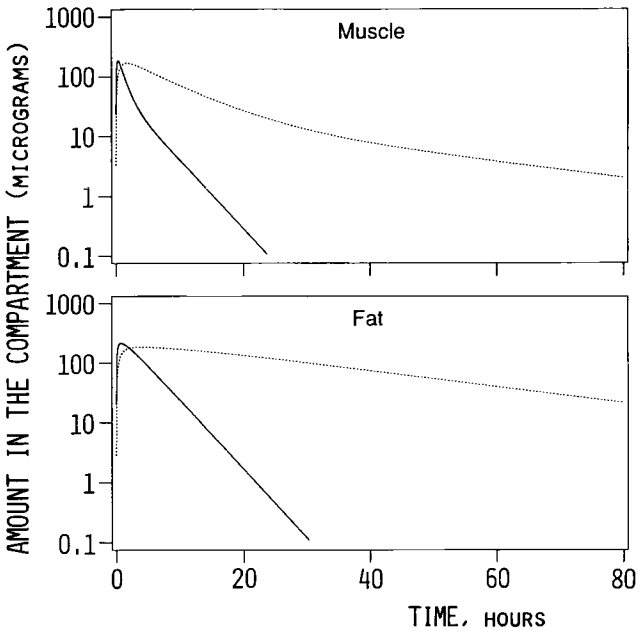

FIG. 3. *B* Computer simulations of the amounts of fentanyl (*dashed curves*) or alfentanil (*continuous curves*) in the muscle and fat compartments after the same bolus injections as in figure 3 A. Note that the time axes have been extended.

which means that the capacity of the tissue for uptake of drug is small in relation to the rate of transfer of drug to the compartment. The drug concentration will therefore peak rapidly. For the same reason, drug will also be removed rapidly from these compartments, which is reflected in the short MTT of the opioids in these tissues (table 2). The muscle and fat compartments represent the opposite. Large apparent volumes are filled with and emptied of drugs by means of limited blood flows. When the drug concentrations peak, muscle and fat together will contain approximately 30% of the injected dose of fentanyl or alfentanil. The organs of the gastrointestinal tract fall into an intermediate category where filling and emptying of the compartments are moderately rapid.

Figure 4 shows simulated arterial plasma concentration curves in a human of fentanyl and alfentanil after bolus doses of 400 and 5,000 μg, respectively. If the simulation is stopped at 24 h, the "terminal" half-life of fentanyl can be estimated at 10–12 h, however, in the next phase it becomes 20 h. This last half-life is determined by the washout of drug from the fat and muscle compartments (fig. 3 B). Alfentanil, on the other hand, attains a terminal half-life of 2.5 h after approximately 3 h.

The differences in pharmacokinetics between fentanyl and alfentanil are apparent in every organ and tissue. Alfentanil partition coefficients were one-half to one-thirtieth those of fentanyl, which would diminish all compartmental volumes and mean transit and residence times correspondingly. Filling and emptying the compartments will consequently be much more rapid with alfentanil than with fentanyl. The brain concentration of fentanyl reaches a transient plateau at around 10 min after the injection, while for alfentanil the concentration peaks sharply in less than 1 min. The washout of alfentanil from muscle and fat is also considerably faster than that of fentanyl, which to a large extent determines the respective elimination half-lives of the two opioids.

Discussion

Measurements in the Rats

The redistribution of fentanyl in the rat from blood and well-perfused organs to muscle and fat has been described by Hug and Murphy,[8] who used tritiated fentanyl to estimate tissue distribution of the drug after a bolus injection. The steady-state drug partitioning we found is in general agreement with the pseudo-steady-state partitioning described by these authors. Our study differs from theirs chiefly in: 1) the use of a long-term infusion to establish steady-state tissue distributions; 2) the simultaneous study of two drugs with similar pharmacologic effects but different physicochemical properties; and 3) the use of a specific chromatographic assay for the drugs.

The disposition of any drug is much faster in rats than in humans, due to the greater cardiac output per unit of

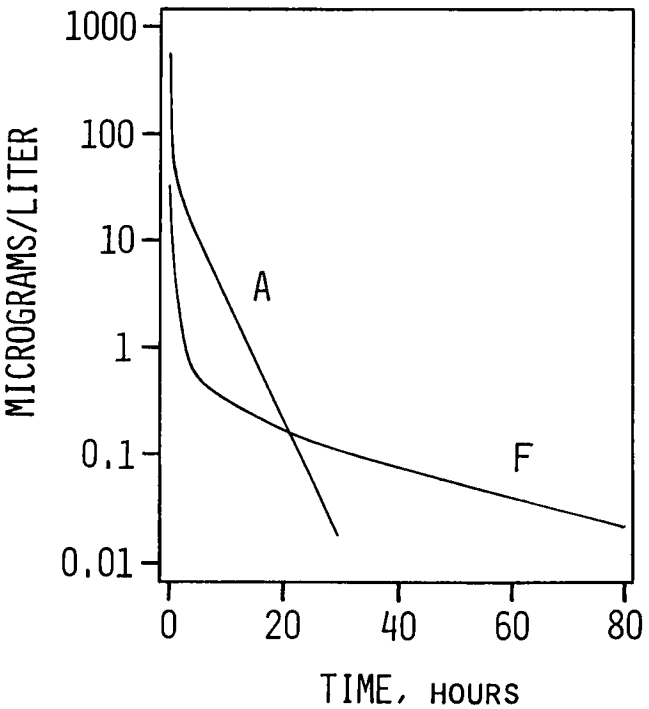

FIG. 4. Simulated arterial plasma concentrations of fentanyl and alfentanil after bolus doses of 400 and 5000 μg, respectively. Note the change in half-life at around 20 h in the fentanyl concentration curve.

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body weight and the higher basal metabolic rate in small animals.[9] Accordingly, the clearance of fentanyl found in the rats was 67 $ml \cdot min^{-1} \cdot kg^{-1}$, which can be compared with the standard liver blood flow (*i.e.*, upper limit of hepatic clearance) in humans of 23 $ml \cdot min^{-1} \cdot kg^{-1}$ (table 2). The longest measurable half-life of fentanyl in our rat strain was 49 min,** which is in close agreement with a previously reported terminal half-life of 45 min in Sprague-Dawley rats.[8] Consequently, the 6-h infusion of fentanyl corresponded to 7.3 terminal half-lives. The equilibration of a drug between tissue and blood is not, however, dependent on the half-life of the drug in blood or plasma, but on the half-life of the drug in the tissue. Assuming a regional blood flow in the fat of 0.18 $ml \cdot min^{-1} \cdot g^{-1}$,[5] the half-life of fentanyl in rat fat can be calculated (as 0.693 × apparent tissue volume ÷ tissue blood flow) to be 116 min. The duration of the infusion was then 3.1 half-lives, which means that the fat may only have reached about 90% of its equilibrium concentration. This estimate may, however, be unduly pessimistic because in the Hug and Murphy experiment,[8] the effective half-life of fentanyl in fat was not much longer than that in plasma. The equilibration of fentanyl in fat would be the slowest one; in all other tissues the equilibration will have been faster, due to higher blood perfusion and lower partition coefficients. With alfentanil the problem of slow equilibration in tissues does not arise. The calculated half-life of alfentanil in fat was 12 min.

We chose to infuse the two drugs simultaneously into the same animals in order to avoid the interindividual variations inherent in a group comparison. Also, fewer animals could be used. The partitioning of the opioids between blood and tissues presumably occurs by passive diffusion, which takes place independently for the two drugs. In keeping with this, a difference in partition coefficients between animals receiving a single drug and those receiving the combined infusion was found only for fentanyl in the liver.

Technical difficulties in determining the partition coefficients in liver may be due to some drug being metabolized immediately after the animals are killed when the blood circulation has stopped.[4] The different values obtained for fentanyl in rats given this drug alone and in rats given the combination of drugs may reflect a metabolic interaction at this stage. In spite of the correction for hepatic clearance in the live animals, the partition coefficients for liver may have been underestimated. Since we could not say *a priori* that the partition coefficient from one group of animals was more "true" than that from the other group, we decided to pool all individual values.

The opioids were infused in pharmacologically active doses. We therefore monitored the rats with respect to respiratory depression, both visually and by arterial blood gas analysis. The moderate acidosis during the experiment could, judging by the data of Meuldermans *et al.*,[10] have increased the unbound fraction of fentanyl from 17% to 18%, which would theoretically result in a 6% overestimation of the tissue/blood partition coefficients of this drug. The unbound fraction of alfentanil is not appreciably influenced by the blood *p*H.[10]

Simulations in Humans

Whole blood was chosen instead of plasma both for simulation of concentrations in humans and for drug assay in the rats because blood concentrations and actual blood flows to organs are more readily related to each other than plasma concentrations and theoretical plasma flows. Also, the whole blood sample is used for assay and less blood needs to be drawn from the animals. Since the equilibration of fentanyl between plasma and blood cells is very rapid[11] and alfentanil does not penetrate into blood cells to any important extent,[10] the drug concentrations in blood and plasma will be proportional at all times. Because the blood/plasma partition coefficient of fentanyl in humans is close to one,[10,11] calculated pharmacokinetic parameters will be the same with blood assay as with plasma assay. For alfentanil, the blood/plasma partition coefficient in humans is 0.63,[10] and consequently, concentrations and the values for clearance and distribution volumes will be different depending on which fluid is assayed. Half-lives, however, will be the same in blood as in plasma.

The results of the simulations in humans are highly dependent on the clearance values used. For fentanyl, the early pharmacokinetic literature contains a bewildering array of conflicting results.[12] However, three recent studies in surgical patients gave consistent values of mean clearance (0.6 l/min) and mean terminal half-life (7.1–8.7 h).[13–15]

In two of these studies,[13,14] blood samples were drawn up to 24 h after a rapid infusion of fentanyl, while the third one[15] used blood sampling during a computer-controlled infusion with an exponentially declining rate. Two studies in volunteers gave clearance values of 1 and 1.5 l/min and terminal half-lives of 3.7 and 3.1 h, respectively.[16,17] The differences between values obtained in patients and volunteers may be the results of comparatively short sampling times (8 and 6 h, respectively) in the volunteer studies leading to an overestimation of clearance. It is, however, reasonable to expect a lowered clearance during anesthesia and surgery due to decreased hepatic blood flow and possible metabolic interactions with concomitantly given drugs. Because the blood flows used in the simulations represent normal physiology we chose

** Unpublished data.

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to use a plasma clearance value of 0.8 l/min for fentanyl in normal humans. Because the blood/plasma concentration ratio for fentanyl in human blood is near unity,[10,11] blood clearance was set equal to plasma clearance.

For alfentanil, the pharmacokinetic data in the literature are more consistent.[1] In our simulations we used a plasma clearance value of 0.344 l/min obtained in volunteers,[17] which also closely agrees with a population pharmacokinetic value in surgical patients.[18] Because the blood/plasma concentration ratio of alfentanil in humans is 0.63,[10] the calculated blood clearance becomes 0.55 l/min. Consequently, the ratio of fentanyl to alfentanil blood clearance estimated in humans became 1.45, which is close to the ratio found in the rats.

Because only 4% of an iv dose of fentanyl,[19] and less than 0.5% of an iv dose of alfentanil,[20] is excreted as unchanged drug in the urine, the renal clearance of the opioids was ignored in the model. Also, the contribution of excretion into the stomach to the total clearance of the opioids in humans has not been adequately quantitated. If, however, some of the supposedly hepatic clearance is due to such excretion it will influence the present model only to a minor degree. The liver concentrations will be lower due to decreased drug input from the "gut" compartment. The hepatic clearance was consequently set equal to total body clearance.

Excretion of fentanyl and alfentanil into the stomach contents of the rats was apparent, and the concentrations found in the stomach walls were probably sums of reversibly distributed drugs in the wall itself and already excreted drugs in the mucosa. The apparent tissue/blood partition coefficients for stomach were therefore not used in the simulation. Instead, the mean partition coefficients for small and large intestine were used to represent reversible distribution to the whole gastrointestinal tract. The excretion of fentanyl into the stomach has also been invoked as an explanation for a secondary peak in the plasma concentration curve of fentanyl after iv administration.[21] However, the low absolute amounts of drug actually secreted and the low bioavailability of enterally absorbed fentanyl weigh heavily against this explanation.[1]

The extensive accumulation and slow washout of fentanyl in the muscle compartment provides a depot of drug that can be mobilized if the perfusion of the muscles increases, *e.g.*, when the patient recovers from anesthesia. This mechanism for the production of a secondary plasma concentration peak has been suggested previously,[16] but quantitative estimates of the drug uptake in muscle in humans have been lacking. The phenomenon is strongly dependent on the high muscle partition coefficient of fentanyl. The tissue depots of alfentanil disappear much faster, and the risk of postoperative renarcotization by this mechanism would appear to be lower with alfentanil than with fentanyl.

The sum of the distribution volumes of fentanyl in organs and tissues given in table 2 is higher than any steady-state volume of distribution in humans reported in the literature: 540 l vs. 422 l,[13] 339 l,[14] and 299 l.[15] This is in keeping with the long terminal half-life after 24 h shown in figure 4. This slow elimination phase has so far not been described in actual pharmacokinetic studies because plasma concentrations of fentanyl have not been determined for more than 24 h after the administration. If this phase can be found in actual patients it will prove also that the volume of distribution at steady-state has been underestimated in currently available studies. This late elimination phase will, however, be of limited clinical significance because the plasma concentration at this stage is far below therapeutic levels.

For alfentanil, the sum of the volumes of distribution becomes 39 l if plasma is assumed as the sampling site, which can be compared with an empirical volume of 35 l in volunteers.[17] The terminal half-life of 2.5 h in the model is also in reasonable agreement with the empirical value of 1.6 h.[17]

Scaling pharmacokinetics from rats to humans can in principle be done in two ways. The first possibility is to use the tissue/blood partition data from rats in humans without modification. The second possibility is to calculate the partition coefficients between tissue and plasma water, *i.e.*, using the unbound concentration instead of total concentration in blood or plasma.[5,22] For lipophilic, basic drugs, good correlations have been found between the volumes of distribution and the tissue/plasma water partition coefficients when different animal species were compared and the use of unbound partition coefficients is generally preferred.[5,22–24] In our case, using the unbound instead of total blood concentration for fentanyl would not have influenced the simulations because the unbound fraction of fentanyl is 17% both in rat blood and in human blood.[10] For alfentanil it does make a difference, the unbound fraction being 15.8% in rat blood and 7.4% in human blood.[10] However, an apparent volume of distribution at steady-state (V_{ss}) of 0.53 l/kg for alfentanil in the rat could be calculated from unpublished data.†† This is close to typical values found in humans.[1,17] It also agrees reasonably well with the sum of distribution volumes in organs and tissues that we calculated from our data in the rat, namely 0.41 l/kg. Alfentanil, which is a very weak base (pK_a = 6.5) with moderate lipid solubility,[1] may not fit into the general pattern for basic drugs. Correcting for the difference in unbound fraction between rats and humans would give an estimated V_{ss} (plasma) of

†† Michiels M, Hendriks R, Michielsen L, Heykants J: Plasma levels and tissue distribution of alfentanil (R 39 209) in the male Wistar rat after a single intravenous dose of 0.16 mg/kg. Janssen Pharmaceutica, Preclinical Research Report R 39 209/13, January 1981.

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18.3 liters. This value is lower than any found experimentally in humans.[1,17] Consequently, the tissue/blood partition coefficients for both fentanyl and alfentanil in the rat were used directly for the simulation in humans.

The amount of drug in the venous compartment is at time zero equal to the dose. After an initial rapid draining, drug that has circulated through the system reappears in the compartment. With fentanyl, this recirculation is slow enough to give a visible secondary peak in the simulated concentration curve. This recirculation peak should not be confused with the secondary peak[21] sometimes seen in studies on surgical patients.

Physiologically, the MTT through a tissue compartment is the average interval of time spent by a drug molecule from its entry into the tissue compartment to its next exit. The MRT in the compartment is the average time spent by a drug molecule in the compartment in all of its passages.[6,25] If MRT $\gg$ MTT, as for instance in the lung compartment (table 2), a majority of the drug molecules will pass through this compartment several times before being eliminated from the body. If, on the other hand, MRT < MTT, as in the poorly perfused tissues, an important proportion of the drug molecules will be eliminated without ever having reached this compartment. Those molecules that do reach the tissue will, however, stay there for a long time. The low blood flows to muscle and fat consequently limit the capacity of these tissues to accumulate the drugs and prolong their terminal half-lives. The sums of the mean residence times in the compartments (11.2 h for fentanyl and 1.87 h for alfentanil) equal the mean residence times of the drugs in the whole system (body).

The impact of the large volume of distribution in the brain of fentanyl compared with that of alfentanil has been discussed in detail by Hug.[3] With equivalent delivery of the opioids in the blood plasma to the CNS, it takes more time to fill up the larger distribution volume of fentanyl and to establish an adequate drug concentration at the receptor sites. This is reflected in the kinetics of the drug effects: for alfentanil the EEG spectral edge was shown to change almost in parallel with the arterial serum concentration, while the EEG changes induced by an iv dose of fentanyl were delayed and prolonged compared with the time course of the serum concentration.[2] As seen in figure 3, it is also reflected in the simulated total brain concentration curves where the maximal concentration of fentanyl is reached at around 10 min and that of alfentanil in less then 1 min. It should, however, be emphasized that the total brain concentration of an opioid is not the same as the receptor site concentration.

In conclusion, measurement of the steady-state tissue/blood partition coefficients of fentanyl and alfentanil in rats gave us a basis to create a physiologic pharmacokinetic model that, as far as can be experimentally verified, approximately describes the disposition of these drugs in humans. In particular it shows how the large difference in tissue partitioning between fentanyl and alfentanil causes the marked overall difference in disposition between these two opioids. The model demonstrates how the depots of drug (especially fentanyl) in muscle and fat govern the terminal half-life of the drug and also creates the possibility of secondary increases in circulating drug concentration during the elimination phase. It also shows the impact of nonspecific tissue binding in the brain on the drug concentration curves in this compartment, which helps to elucidate the difference in effect kinetics between fentanyl and alfentanil.

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Appendix

The multicompartmental model selected to simulate fentanyl and alfentanil disposition in humans resembles the flow-limited physiologic model proposed by Bischoff.[26] It makes the following assumptions: 1) the body is represented by a time-invariant model; 2) tissues, arterial blood, and venous blood are represented by well-stirred compartments; 3) transfer of drug between compartments are first-order processes; 4) elimination of drug occurs only in the liver (renal excretion and secretion into the stomach are supposed to be negligible); 5) rate constants for the first-order processes described in above (3) are related to physiologic (independently measured) quantities (organ volumes and blood flows); and 6) the partition coefficients for the tissues in the model (see below) are equal to the (independently measured) steady-state partition coefficients. Figure 1 shows the structure of the multicompartment model adopted. The mass balance equations are as follows.

Arterial blood (a):

$$V_a d\frac{C_a}{dt} = Q_B C_{lu}/R_{lu} - \sum_i Q_i C_a \quad (1)$$

where V_a is the volume of a, C_a is the drug concentration in a, Q_B is total blood flow (*i.e.*, $\sum_i Q_i$), C_{lu} is the drug concentration in the lung, R_{lu} is the partition coefficient (see below) in the lung, and Q_i is arterial blood flow to the tissue (i). The sum in i extends to all the tissues receiving drug from arterial blood.

Noneliminating tissue (i):

$$V_i d\frac{C_i}{dt} = Q_i(C_a - C_i/R_i) \quad (2)$$

where C_i, V_i, and R_i are, respectively, drug concentration, volume, and partition coefficient of the tissue (i).

Eliminating tissue: liver (li):

$$V_{li} d\frac{C_i}{dt} = (Q_{li} - (Q_g + Q_s + Q_p))C_a + Q_g C_g/R_g + Q_s C_s/R_s + Q_p C_p/R_p - Q_{li} C_{li}/R_{li} - CL_{li0} C_{li}/R_{li} \quad (3)$$

where the subscripts g, s, and p indicate gut, spleen, and pancreas, and the clearance of drug in the liver is expressed as CL_{li0}/R_{li}.

Venous blood (v):

$$V_v d\frac{C_v}{dt} = -Q_B C_v + \sum_j Q_j C_j/R_j \quad (4)$$

The sum in j extends to all tissues giving drug to the venous blood.

Lung tissue (lu):

$$V_{lu} d\frac{C_{lu}}{dt} = Q_B C_v - Q_B C_{lu}/R_{lu} \quad (5)$$

For each tissue (i) at steady-state (*i.e.*, $dC_i/dt = 0$), the ratio of C_i to C_a equals R_i. The partition coefficient parameter R_i is assumed to be equal to the partition coefficient ($R_i$ss) measured in the steady-state experiment. For the liver, under assumptions 4 and 6, an estimate of CL_{li0} and R_{li} can be obtained from the steady-state partition coefficient of the liver (R_{li}ss) and an estimate of total blood body clearance (TBC), as follows.

$$CL_{li0} = \frac{Q_{li} \cdot TBC}{Q_{li} - TBC} \quad (6)$$

$$R_{li} = \frac{Q_{li} + CL_{li0}}{Q_{li}} R_{li}ss \quad (7)$$

Given values for the parameters, a selected drug input, locus of input (the venous compartment), and time range, the differential equations above with the input function can be integrated to give concentrations of drug in different tissues as a function of time. To do so, a computer program that drives the differential equation solver DVERK (IMSL, NB Building, 7500 Bellaire Boulevard, Houston, Tx) was adopted.

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