First Pass Uptake of Fentanyl, Meperidine, and Morphine in the Human Lung

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The first pass uptake of fentanyl, meperidine, and morphine in human lung was studied in patients using a double indicator dilution technique. A bolus containing one of the drugs and indocyanine green dye (ICG) was rapidly injected into the central venous catheter of patients prior to anesthesia for surgery. Sequential arterial blood samples were collected at 1-s intervals for 45 s after injection. The total amount of drug taken up by the lung during the first pass and the instantaneous extraction of drug at each time point during the first pass were calculated from the differences in the arterial blood concentration *versus* time curves of the nondiffusible indicator (ICG) and the drug. The total uptake (mean ± SE) during the first pass through the human lung for fentanyl and meperidine was 75.2 ± 3.2% and 64.7 ± 7.8% of the injected dose, respectively. The pulmonary uptake of morphine was very small, with 96.5 ± 7.1% of the injected dose recovered in arterial blood after the first pass through the lung. The arterial blood concentration of drug and dye *versus* time showed a slight delay of the fentanyl and meperidine peaks compared to ICG. It was also observed that greater than 90% of these drugs were extracted from the blood in the early part of the first pass, but the extraction decreased with time during the first pass through the lung. These findings indicate that some of the drug taken up by the lung can diffuse back out into the blood. In spite of this back diffusion, 75% and 65% of the fentanyl and meperidine remained in the lung tissue at the end of the first pass. This high first pass pulmonary uptake of fentanyl and meperidine results in a large decrease in the amount of drug that enters the systemic circulation immediately after injection. This non-respiratory pulmonary function could play a major role in determining the plasma pharmacokinetics of these drugs immediately after intravenous administration. No such role of the lung exists for morphine. (Key words: Analgesics: fentanyl; meperidine; morphine. Anesthetics, intravenous: fentanyl; meperidine; morphine. Lung: drug uptake. Pharmacokinetics.)

IT IS NOW WELL ACCEPTED that the pulmonary circulation has important functions other than gas exchange. This includes a pharmacokinetic function in which cells in the pulmonary vascular bed have been shown to accumulate a variety of vasoactive endogenous substances and a large number of exogenous drugs.[1-5] Animal studies have shown high pulmonary accumulation of amine drugs, with lung tissue to plasma drug concentration ratios as high as 400.[4] Studies in isolated perfused animal lung (IPL) preparations indicate that uptake of certain drugs is rapid, extensive, saturable, and results from passive diffusion of the drug from the plasma into lung tissue.[6-14] The extent of uptake appears to depend mainly on the physicochemical characteristics of the drug with basic amines (pK > 8.0) of moderate to high lipid solubility accumulating in pulmonary tissue to the greatest extent.[6,7,10,11]

Because the lung receives the entire cardiac output, has a large capillary surface area, and is uniquely situated at the head of the systemic circulation, it could play an important role in regulating the arterial blood concentration of compounds which exhibit high pulmonary accumulation. Few studies have attempted to examine this potential role of the lung in man. Gillis *et al.* studied the first pass pulmonary extraction of norepinephrine and 5-hydroxytryptamine in patients before and after cardiopulmonary bypass, and developed a radiolabeled double indicator dilution method to accurately quantify the extent of first pass pulmonary extraction.[15-17] Geddes *et al.* used a double indicator dilution method to determine the total first pass uptake of propranolol in cardiac catheterization patients, and found that 75% of the propranolol was taken up by the lung during the first pass.[18] Jorfeldt *et al.* used a non-radioactive double indicator dilution technique to study the first pass uptake of lidocaine in the human lung.[19-20] They found that 60% of the lidocaine bolus was extracted by the human lung during the first pass.

The extensive first pass pulmonary uptake of these basic lipophilic amines supports the concept of a significant role for the lung in modulating the early pharma-

cokinetics of some drugs after intravenous administration. The purpose of the present study was to examine the first pass pulmonary uptake of fentanyl, meperidine, and morphine in conscious patients. These narcotic analgesics are commonly used to induce or supplement general anesthesia, and represent a series of basic lipophilic amines with different physicochemical properties.

Materials and Methods

PATIENT SELECTION

Nineteen ASA physical status I–III subjects were studied prior to elective surgery. All studies were approved by, and performed in accordance with, institutional policies on human experimentation, and informed consent was obtained from each patient. In none of the patients was evidence of severe or moderate obstructive or restrictive lung disease revealed by clinical examination, chest x-ray, and by pulmonary function tests on the day prior to surgery. The patients were divided into three groups according to drug studied.

Direct arterial blood pressure (radial artery), electrocardiogram (chest lead V_5) and a central venous pressure catheter or pulmonary artery catheter were utilized for monitoring purposes, drug injections, and sample withdrawals. Preoperative medication was limited to 10 mg diazepam or 2 mg lorazepam po. Characteristics of the patients are shown in Table 1.

MEASUREMENT OF PULMONARY FIRST PASS UPTAKE

The first pass uptake of fentanyl, meperidine, and morphine was determined using a double indicator dilution technique similar to the method described by Jorfeldt et al.[19] Indocyanine green (ICG) (Cardiogreen H.W.D., Baltimore) was used as the nonextractable vascular indicator. A 3-ml bolus solution was prepared containing ICG (15 mg), human serum albumin (62 mg), and fentanyl (112 μg), meperidine (37.5 mg), or morphine (15 mg). The human serum albumin was necessary to prevent precipitation of the ICG by the basic drugs. This solution was prepared immediately before use, and a 2.0-ml bolus was loaded into a 2-ft length of plastic catheter connected to the central venous catheter. The ICG-drug bolus was injected within 2 s with a 10-ml saline flush. The remaining 1.0 ml of ICG-drug injectate was saved for preparation of standard curves for ICG and drug analysis. Blood was withdrawn from the radial artery (60 cc/min) by a peristaltic pump (Master Flex, Cole-Palmer) and collected in 1-s fractions in a specially modified Gilson Escargot fraction collector. Tubes in the fraction collector contained 25 μl of

heparine (10,000 units/ml). A total of 45 blood samples were collected from the time of injection.

ANALYTICAL METHODS

The first eight 1.0-ml blood samples after injection of the ICG-drug solution did not contain dye or drug, and were used to prepare standard curves for quantification of the ICG and the particular drug by adding various amounts of the remaining injectate solution to these blood samples.

All 1.0-ml blood samples were then diluted with 4.0 ml of water and vortexed vigorously to lyse the red cells. After centrifugation (20 min, 1000 × g), the samples were decanted into disposable spectrophotometry cuvettes and the ICG concentration determined from its absorbance at 805 nm. At this point, the samples could be frozen at $-20°$ C until drug analysis.

Fentanyl blood concentrations were determined by specific radioimmunoassay (RIA) in a manner similar to that described in a previous study.[21] The fentanyl RIA is based on the method of Michiels et al.,[22] and is commercially available from the Institut National Des Radioelements, Belgium. Each diluted blood sample was assayed in duplicate using the standard curve prepared from the original injectate solution. The assay was then carried out according to the manufacturer's protocol, except that 100 μl of 30% H_2O_2 was added to decolorize the final RIA supernatant and increase tritium counting efficiency. The lower limit of sensitivity of the assay was 0.25 ng/ml of fentanyl in whole blood, with a coefficient of variation of 10%.

Morphine blood concentrations were determined by a morphine specific RIA (Morphine Coat-A-Count, Diagnostic Products, Inc.). The assay was used according to the manufacturers suggested protocol, except that the standard curve was prepared as described above. Due to the high sensitivity of the morphine RIA (1–100 ng/ml), the 1-s blood samples were further diluted 1:100 prior to analysis. Each blood sample was assayed in duplicate with a lower limit of sensitivity of 1 ng/ml of morphine in whole blood and a coefficient of variation of 6%.

Meperidine was assayed by a gas chromatography (GC) method developed in our laboratory. Three milliliters of the diluted blood sample was placed in a 6-ml teflon stoppered glass tube, followed by the addition of 100 μl of internal standard solution (etidocaine 0.15 mg/ml) and 0.3 ml of 6 N trichloracetic acid. The tubes were mixed by vortexing and centrifuged at 1000 × g for 10 min. The clear supernatant was withdrawn and placed in a clean 12-ml conical centrifuge tube with a teflon lined screw cap. After addition of 1.0-ml of 5 N NaOH and 200 μl of carbon disulfide, the tubes were placed in a reciprocating shaker for 10 min and then
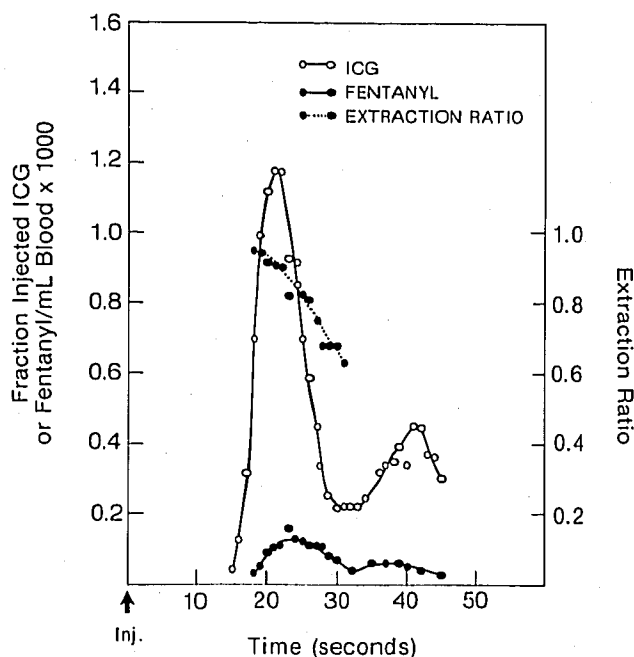
FIG. 1. Fraction of injected dose (solid lines) of ICG and fentanyl per ml of arterial blood *versus* time (seconds) after intravenous injection of the dye-drug bolus. Dashed line represents the extraction ratio for fentanyl with time. Difference in area under the ICG and fentanyl curves at 95% ICG recovery indicate 86.6% uptake of fentanyl during the first pass through the lung. Initial extraction (ER) of fentanyl was 94.7%, and the times to peak ICG and fentanyl concentrations were 21 s and 23 s, respectively, after injection.

centrifuged at 1000 × g for 10 min. The CS_2 formed a stable layer at the bottom of the conical tube, and 2-μl samples for injection into the GC were withdrawn by carefully inserting the microsyringe needle through the aqueous layer into the CS_2 layer.

A Hewlett Packard® Model 5880A gas chromatograph equipped with a flame ionization detector was used for meperidine determinations. The glass column was a 2 m long × 2 mm ID packed with 3% OV-17 on 120 mesh Chromsorb W. Nitrogen at 30 ml/min was used as a carrier gas, and the hydrogen and air flow rates were 30 and 240 ml/min, respectively. Meperidine and etidocaine were separated using a temperature program with an initial temperature of 210° C (rising to 240° C at 8 degrees/min). Injection port and detector temperatures were 250° and 300°, respectively. In this system, the absolute retention times of meperidine and etidocaine internal standard were 2.2 and 4.1 min, respectively. The area under the peaks was measured and the peak area ratios between the internal standard and meperidine used to quantify the amount of meperidine by comparison with the standard curve. A linear standard curve was obtained for meperidine concentrations of 0.2–100 μg/ml. The minimum sensitivity was 0.2

μg/ml meperidine in whole blood with a coefficient of variation for the assay of 7%.

CALCULATIONS

Total uptake of each drug in the first pass through the human lung is based on comparison to the nonextractable indicator ICG, as described by others.[18–20] The amount of dye or drug per ml of blood was divided by the total amount of each injected and expressed as the fraction of injected drug recovered in each 1-s arterial blood sample (figs. 1–3). The ICG curve represents the fraction of the injected dose *versus* time curve where no extraction by the lung occurs, and the difference in area under this dye curve and the drug curve is equal to the total fraction of injected drug that was extracted from the blood into the lung during the first pass. To calculate the total area under the first pass curve, semilogarithmic plots of the linear descending part of the curve were extrapolated to determine the fractions of injected dose in the blood per second had there been no recirculation.[19,23] For comparative purposes, the percent of drug taken up into the lung was calculated at the time when 95% of the injected ICG had passed through the lung, as described by Jorfeldt *et al.*[19]

FIG. 2. Fraction of injected dose (solid lines) of ICG and meperidine per ml of arterial blood *versus* time (seconds) after intravenous injection of the dye-drug bolus. Dashed line represents the extraction ratio for meperidine with time. Difference in area under the ICG and meperidine curves at 95% ICG recovery indicated 80.7% uptake of meperidine during the first pass through the lung. Initial extraction (ER) of meperidine was 93.1%, and the times to peak ICG and fentanyl blood concentrations were 23 s and 27 s, respectively, after injection.

The extraction ratio represents the fraction of drug in blood taken up into the lung at each time point (instantaneous extraction ratio). The extraction ratio was calculated by the formula:

$$E_R = 1 - \frac{F_{drug}}{F_{ICG}},$$

where F is the fraction of injected ICG or drug in arterial blood at each 1-s time point after injection.[19,23]

The cardiac output was measured by indicator dilution from the ICG curves for each patient, as described by Guyton.[24] The cardiac output (CO) was calculated by the formula:

$$CO = \frac{60}{A_{ICG}},$$

where A_{ICG} is the total area under the curve of fraction injected ICG per ml versus time in second.

Analysis of variance and Duncans multiple range test were used for statistical comparisons.

Results

The body weight, age, and cardiac output for the three groups of patients are shown in table 1. The CO was calculated from the ICG-dye dilution curve and ranged from 3–7 l/min for patients in the study. No significant differences in CO were observed between the three patient groups, and there was no apparent correlation between CO and the first pass uptake for a given drug. Age and body weight were similar between the fentanyl and meperidine groups; however, they were slightly higher in the four patients in which morphine uptake was studied. Our studies with morphine were limited to only four patients, since, as will be shown, the first pass uptake of morphine in the human lung was very small.

Figures 1, 2, and 3 show typical first pass uptake curves in the human lung for fentanyl, meperidine, and morphine, respectively. Each figure represents the fraction of the injected ICG and respective drug per ml of blood in the 1-s blood samples with time after injection of the dye-drug bolus. Because cardiac outputs for
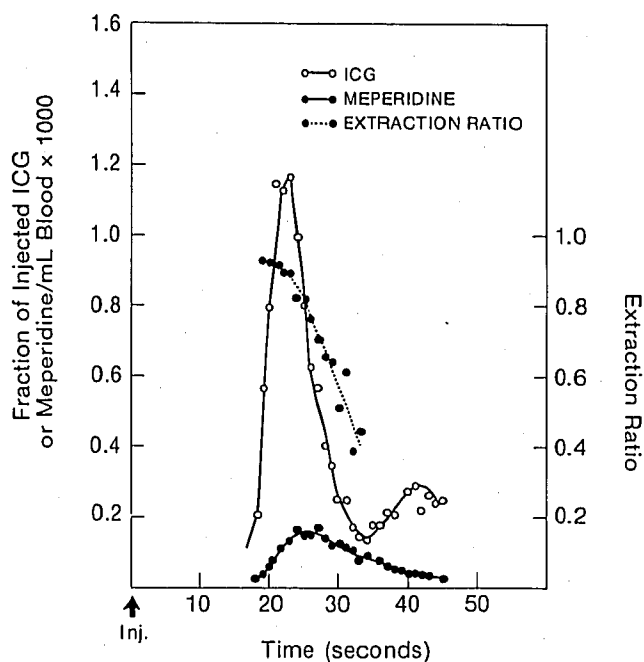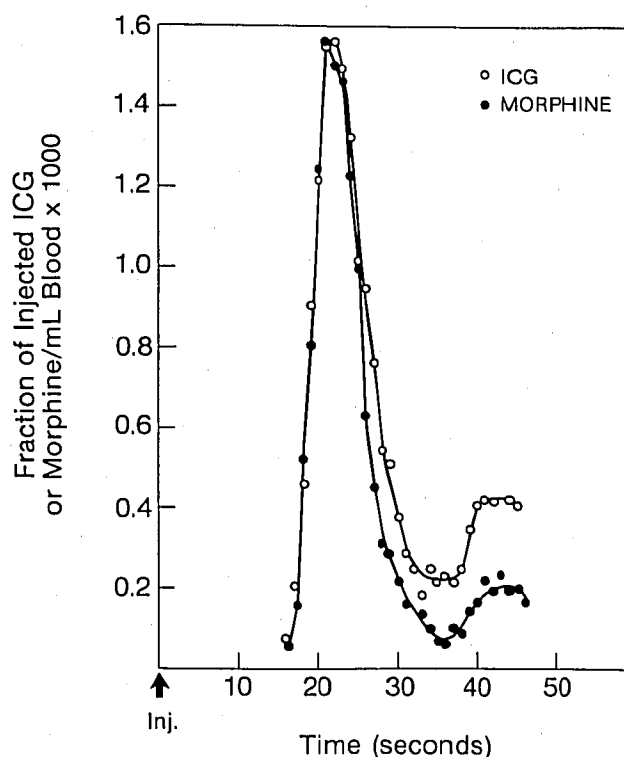

FIG. 3. Fraction of injected dose of ICG and morphine per ml of arterial blood versus time (seconds) after intravenous injection of the dye-drug bolus. Difference in area under the ICG and morphine curves at 95% ICG recovery indicated that 92.5% of the morphine remained in the blood after the first pass through the lung.

each patient within a group differed, it is not possible to express the fraction of injected ICG or respective drug with time as a mean for all patients in the group. The data in figures 1, 2, and 3, therefore, are from single patients in each group, and represent the type of curve observed for that drug.

For all three groups, the ICG curve peaked between 19–24 s after injection of the dye-drug bolus, with a second peak at 40–42 s representing the second pass of the ICG through the lung. Comparison of the fraction of injected ICG and fentanyl recovered in arterial blood samples (fig. 1) demonstrated an extensive first pass up-

TABLE 1. Summary Data for First Pass Pulmonary Drug Uptake

Drug	N	Total Dose	Age (Yr)	Body Weight (kg)	CO (Liters/min)	Lung Uptake (% Injected)	Peak Delay (S)
Fentanyl	8	75 μg	56.4 ± 5.4	80 ± 5	5.42 ± .55	75.2 ± 3.2	2.44 ± .59
Meperidine	7	25 mg	58.3 ± 2.8	78 ± 5	6.58 ± .51	64.5 ± 7.8	3.64 ± .30
Morphine	4	10 mg	70.8 ± 2.8	89 ± 7	5.65 ± .57	3.5 ± 7.1	–0–

Data for age, weight, CO, lung uptake, and peak delay represent the mean ± SE for each group of patients. N is the number of patients per group. CO was calculated from the ICG dye dilution curves as described. The lung uptake is the percent of the injected dose remaining in the lung after 95% of the ICG has passed through the lung. The peak delay is the difference in seconds between the time of peak blood concentration of the ICG and the drug during the first pass through the lung.

take of fentanyl in the human lung. For the patient shown, the data indicated that 86.6% of the fentanyl was taken up by the lung during the first pass. For all eight patients in this group, first pass uptake of fentanyl ranged from 63–87%, with a mean ± SE first pass uptake of 75.2 ± 3.2%. The extraction of fentanyl was very high (greater than 90%) in the initial part of the first pass through the lung. The extraction ratio decreased but remained positive during the remaining portion of the first pass (fig. 1). This apparent decrease in extraction ratio suggests diffusion of some of the accumulated fentanyl back out of the lung into the blood, although the net flux of fentanyl is still into the lung during the first pass. The presence of some back diffusion is also indicated by a delay of 2–4 s (mean 2.4 s, table 1) in the peak concentration of fentanyl in arterial blood as compared to the ICG peak. In spite of this indication that some back diffusion occurs, 75% of the injected fentanyl remains in the lung at the end of the first pass.

Figure 2 shows that 80.7% of the meperidine injected was extracted from the blood by the lung during the first pass. Somewhat greater variability was observed in the meperidine in the seven patients studied, and ranged from 40–85% of the amount injected, with a mean ± SE uptake of 64.5 ± 7.8%. Like fentanyl, meperidine extraction was initially high, greater than 90%. Again, some back diffusion was indicated by the decrease in the extraction ratio with time (fig. 2) during the first pass and the slight delay (3.6 s) in the meperidine concentration peak as compared to ICG (table 1).

The first pass uptake of morphine in the human lung (fig. 3), ranged from 0–20% of the injected dose. Because of the very small mean uptake of morphine (<4%) observed, the first pass is more accurately described by the fraction of injected drug recovered in the arterial blood samples. In the patient data shown, 92.5% of the injected morphine was recovered in arterial blood. The mean ± SE recovery in arterial blood for all four patients studied was 96.5 ± 7.1% of the amount injected. Extraction ratios were not calculated due to low pulmonary accumulation. With morphine, we did observe a second peak in the fraction of injected drug *versus* time curve, representing a second pass through the lung as observed with ICG. Such a second pass peak for fentanyl and meperidine was not prominent because of the high uptake in the first and subsequent pass through the lung, as well as other organs.

Discussion

The present study demonstrates the very high capacity of the human lung to extract certain drugs from the

blood. This uptake is rapid, with extraction ratios exceeding 0.9 in the early part of the uptake curves with mean first pass uptakes of 75.2% and 64.5% for fentanyl and meperidine, respectively. The high accumulation of fentanyl and meperidine, together with the high first pass uptake in the human lung reported for lidocaine[19,20] and propranolol,[18] suggests that concentration of basic lipophilic amines by human lung tissue is similar to that observed in animal models.[4,6–16] The data presented here can also be interpreted to support the idea that the extent of pulmonary uptake of amine drugs is related to physicochemical properties, such as lipid solubility and basicity of the amine nitrogen. As judged from octanol-water partition coefficients, fentanyl and meperidine are 676 and 28 times more lipid soluble than morphine. Also, morphine is a less basic amine (pKa = 7.9) compared to fentanyl (pKa = 8.4) and meperidine (pKa = 8.5).[25,26] Together, these physicochemical differences may account for our finding that first pass pulmonary uptake of morphine in man was only a few percent of the injected dose, compared to 75% and 65% for the more lipophilic fentanyl and meperidine, respectively.

In addition to physicochemical properties, plasma protein binding of fentanyl, meperidine, and morphine could be a factor in the extent of pulmonary accumulation, since it must be the unbound drug that is taken up into the lung tissue. Meuldermans *et al.*[26] determined that the free fraction of fentanyl, meperidine, and morphine in human plasma was 16%, 30%, and 70%, respectively. This order is exactly opposite the order of extent of first pass uptake in the human lung, suggesting that the degree of plasma protein binding of these basic lipophilic amines has little influence on the extent of pulmonary accumulation. A similar result was observed in our rat IPL studies, in that the presence or absence of 4.5% bovine serum albumin (BSA) in the artificial perfusate had little effect on the pulmonary uptake of the basic lipophilic amine methadone (40% bound to BSA).[14] One possible explanation for our finding is that the affinity of basic lipophilic amines is much greater for lung tissue than plasma protein.

An important aspect of the high first pass pulmonary uptake observed for fentanyl and meperidine is the effect of such uptake on their plasma pharmacokinetics. Certainly, extraction of 75% and 65% of these drugs from the blood during the first pass through the lung results in a significant reduction in the transient peak plasma levels to which other organ systems are exposed. Had no pulmonary uptake occurred, theoretical peak blood concentrations for each drug can be calculated from the ICG dye peak (figs. 1, 2) and the amount of each drug injected. Comparison with actual peak blood concentrations reveals that uptake into the lung during

the first pass lowers peak blood concentrations of fentanyl and meperidine by six- and four-fold, respectively. Considering the total amount of drug removed from the circulation and the large reduction in peak blood levels as a result of first pass uptake of fentanyl and meperidine in the lung, this non-respiratory pulmonary function would limit the rate at which the injected drug actually enters the systemic circulation immediately after intravenous administration.

The effect of first pass pulmonary uptake on the pharmacokinetics of fentanyl and meperidine at longer times after intravenous administration is dependent not only on the amount of drug taken up by the lung, but also on the rate at which accumulated drug diffuses out of the lung. The data indicate that some of the accumulated fentanyl and meperidine diffused out of the lung back into the blood during the first pass. Because of the short duration of blood sample collection (45 s) and the second pass through the lung, the rate of this back diffusion cannot be quantified from these experiments. Even in the presence of some back diffusion, 75% and 65% of the injected fentanyl and meperidine remained in the lung tissue at the end of the first pass. Work by Taeger et al.[27] provides some insight into the rate of diffusion of accumulated fentanyl out of the lung and back into the blood after the first pass through the lung. Taeger et al. measured the difference in arterial and venous blood concentration of fentanyl for 14 min after the first pass through the human lung, and estimated that 60% of the fentanyl accumulated during the first pass diffused back out of the lung during the first 10 min. Based on our measurements, 25% of the injected fentanyl enters the systemic circulation immediately after injection, and, together with the estimate by Taeger et al., another 45% of the injected dose would be delayed and gradually enter the systemic circulation over the next 10 min. The remaining 30% of the injected dose of fentanyl would diffuse out of the lung at a slower but unknown rate. In view of these estimates, the first pass pulmonary uptake of fentanyl may play a significant role in at least the early pharmacokinetics of fentanyl. The early phase of plasma drug disappearance after intravenous administration is thought to represent distribution to, and uptake by, other tissues. Depending on the type of kinetic model used, the early part of the distributional plasma half-life of fentanyl has been estimated at between 1.2–4 min.[25] In view of the extensive first pass uptake and the data of Taeger et al.,[27] this earlier rapid plasma disappearance of fentanyl may be complex, reflecting: 1) disappearance of drug due to uptake by other tissues, moderated by; 2) an addition of drug to plasma from the large pulmonary pool. The fact that plasma concentrations of fentanyl are decreasing during this time period does mean that the rate of up-

take into other tissues exceeds the rate of efflux from the lung.

Hug has reviewed plasma pharmacokinetic data for fentanyl and meperidine, and both drugs exhibit a terminal plasma disappearance phase with a half-life of 3–4 h.[25] This terminal phase is attributed to metabolism and elimination of these drugs, and we assume the reduced pulmonary pool acts like other tissue reservoirs, responding to changes in plasma concentration as elimination occurs.

Another important aspect of pulmonary drug accumulation is that of saturation of uptake in the lung. The uptake of basic lipophilic amines by the lung is thought to be non-specific, resulting from simple diffusion, with the initial rate of uptake dependent on the rate at which the drug is supplied to the lung.[4,8,12] It is unlikely that the very rapid translocation from blood into the lung tissue is saturable; however, the lung pool or compartments that interact with the drug must be finite. Jorfeldt et al.[19,20] found no evidence of saturability in the first pass accumulation of lidocaine in the human lung. Geddes et al., on the other hand, found that the first pass uptake of propranolol decreased from 75% to 33% in patients on chronic propranolol therapy, suggesting that lung uptake of propranolol is partly saturable by normal oral doses.[18]

It is unlikely that saturation of pulmonary uptake of fentanyl could be observed in the human lung, due to the small absolute mass of this potent analgesic normally used in induction of anesthesia. In addition, high first pass uptakes (>80%) of meperidine were observed in some patients where the total mass of injected amine was more than 300 times that of fentanyl. With morphine, however, the very low first pass uptake could be viewed as saturation of the capacity of the lung to accumulate this amine. To provide further insight into this, it will be necessary to study the first pass uptake of very low doses of morphine.

The nonspecific nature of pulmonary accumulation of basic lipophilic amines suggests that accumulation of one drug could saturate the capacity of the lung, resulting in a decreased uptake of a second basic lipophilic amine. This has been demonstrated in isolated perfused animal lung preparations,[7] and provides a potential mechanism of a drug-drug interaction that could alter the initial pharmacokinetics of drugs with high pulmonary extraction. In man, Jorfeldt et al. were unable to detect any effect of prior administration of mepivicaine on the first pass uptake of lidocaine; however, their data suggest that lidocaine displaced mepivicaine from the lung.[19,20] Recently, we presented evidence in the rat IPL that pre-perfusion of the lung with propranolol decreased the pulmonary accumulation of fentanyl.[28]

There are other situations that could also alter pul-

monary uptake and, thus, the pharmacokinetics of a drug. For example, lung injury, whether acute (infection, pulmonary edema, aspiration pneumonitis) or chronic (restrictive, or obstructive lung disease), could potentially alter pulmonary drug uptake. Gillis *et al.* suggested that changes in the pulmonary uptake of a 5-hydroxytryptamine might be useful to detect early damage to human endothelium before clinical signs of pulmonary damage are evident.[15,16] Pany *et al.* have suggested using propranolol uptake in the human lung in a similar manner, since they found that uptake was reduced in the early stages of shock, indicating that propranolol was a sensitive index of pulmonary endothelial damage.[23] Altered pulmonary blood flow could also change the role of the lung in moderating the early pharmacokinetics of a drug. Pany *et al.* reported that pulmonary uptake of propranolol was independent of cardiac output in the dog, but decreased during partial occlusion of the pulmonary circulation.[23]

In conclusion, the rapid and very high first pass uptake of intravenous fentanyl and meperidine in man suggests that the lung could play a major role in at least initial plasma pharmacokinetics of these drugs. No such role is apparent for morphine.

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