Effect of Propranolol on the First Pass Uptake of Fentanyl in the Human and Rat Lung

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The first pass uptake of fentanyl in the human lung was studied in two groups of patients using a double indicator dilution technique. A bolus containing fentanyl and indocyanine green dye (ICG) was rapidly injected into the central venous catheter of patients prior to anesthesia. Sequential arterial blood samples were collected at 1-s intervals for 45 s after injection. The total amount of fentanyl taken up by the lung during the first pass and the instantaneous extraction of fentanyl 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. In patients who had been receiving no other drugs prior to the experiment, the total first pass uptake (mean ± SE of fentanyl was 82.6% ± 1.4% of the injected dose. In patients who had been receiving 50–120 mg/day of propranolol the total first pass uptake (mean ± SE) of fentanyl decreased to 52.8% ± 6.3% of the injected dose. In one patient on 120 mg of propranolol per day, first pass uptake of fentanyl was only 20.3% of the injected dose. Additional studies in a rat isolated perfused lung preparation copulsed with fentanyl and propranolol also demonstrated that one basic lipophilic amine (propranolol) could inhibit the pulmonary uptake of a second basic lipophilic amine (fentanyl). The high first pass uptake of fentanyl in the human lung limits the rate of entry of this drug into the systemic circulation. In patients receiving chronic propranolol therapy two to four times as much of the injected fentanyl enters the systemic circulation in the time period immediately after injection. This represents a potential mechanism of a drug–drug interaction that could have pharmacokinetic, pharmacodynamic, and clinical significance. (Key words: Analgesics: fentanyl. Anesthetics, intravenous: fentanyl. Drug interactions: fentanyl; propranolol. Lung: drug uptake. Pharmacokinetics.)

A variety of vasoactive endogenous substances and a large number of exogenous substances are taken up into lung tissue on passage through the pulmonary circulation.1–5 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 that exhibit high pulmonary accumulation. Animal studies have shown that high pulmonary accumulation of many drugs depends mainly on the physicochemical properties of the drug, with basic amines (pKa > 8.0) of moderate to high lipid solubility accumulating in pulmonary tissue to the greatest extent.6–8 Studies in isolated perfused animal lung (IPL) preparations have shown that the pulmonary uptake of basic lipophilic amines is rapid, extensive, saturable, and results from simple diffusion of the drug from the plasma into the tissue.9–14 Saturability of uptake can result in competition between basic lipophilic amines for pulmonary drug accumulation sites as has been demonstrated in animal IPL-preparations.7

Extensive first pass uptake of the basic lipophilic amines lidocaine,15–17 propranolol,18 fentanyl,19,4 and meperidine19 has been demonstrated in the human lung. We reported that 76% of injected fentanyl and 60% of the injected dose of meperidine was taken up in the first pass through the human lung.19 Any condition that inhibits this high first pass uptake would allow a greater portion of the injected dose to reach the systemic circulation during the first pass and would alter the early distribution phase of plasma pharmacokinetics and possibly the onset of pharmacologic action. The nature of drug uptake in the lung suggests that one drug might alter the uptake of a second basic lipophilic amine, thus providing a potential mechanism of a drug–drug interaction. The impact of chronic administration of a drug on its own first pass pulmonary uptake has been examined. Geddes et al.18 found that the first pass pulmonary uptake of propranolol in humans was reduced from 80% to 33% of the injected dose in patients receiving chronic propranolol therapy.

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The purpose of the present study was to investigate the possibility that propranolol therapy may also decrease the high first pass uptake of a second basic lipophilic amine. To this end, we determined the first pass uptake of fentanyl in patients receiving chronic propranolol therapy.

**Methods**

Sixteen ASA PS 1–3 subjects were studied prior to elective surgery. All studies were approved by and performed in accordance with the institutional policies on human experimentation, and informed consent was obtained from each patient. In none of the patients was there evidence of severe or moderate obstructive or restrictive lung disease revealed by clinical examination, chest x-ray, or pulmonary function tests on the day prior to surgery. The patients were divided into two groups: the control group, which prior to surgery received no other drugs, and the group that received a daily dose of propranolol of 80 to 120 mg/day for at least 1 month prior to surgery. Because these studies were carried out simultaneously with our previous published studies on the first pass uptake of fentanyl, the last five patients from the previous study and two additional patients not receiving propranolol make up the control group for the present study.

Direct arterial blood pressure (radial artery), electrocardiogram (chest lead V5), and central venous catheter or pulmonary artery catheter were utilized for monitoring purposes, drug injection, 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 was determined using a double indicator dilution method as previously described. Briefly, indocyanine green (ICG) (Cardiogreen, H.W.D., Baltimore, Maryland) 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). Two milliliters of this solution was immediately loaded into a 3-ft length of plastic catheter connected to the central venous catheter. The ICG–fentanyl bolus was injected within 2 s with a 10-ml saline flush. The remaining 1.0 ml of ICG–fentanyl injec- jectate was saved for preparation of standard curves for ICG and fentanyl analysis. Blood was withdrawn from the radial artery (60 ml/min) by a peristaltic pump (MasterFlex, Cole-Palmer) collected in 1-s fractions in a specially modified Gilson Escargot fraction collector. The fraction collector tubes contained 25 μl of heparin (10,000 U/ml). A total of 45 blood samples were collected from the time of injection.

**Single Pass Perfusion in the Isolated Rat Lung**

The uptake of fentanyl in the presence and absence of propranolol was also determined during a single pass perfusion of the isolated perfused rat lung (IPL). Male Sprague-Dawley rats (300–400 g), obtained from King Animal Laboratories (Oregon, Wisconsin) were housed for 1 week in air-conditioned (23°C) quarters on a 12-h light/dark cycle with free access to food and water prior to an experiment. The surgical procedures and isolated perfused rat lung preparation have been described previously. Briefly, once the lung is removed from the thorax (pentobarbital anesthesia), the lung is suspended by the arterial and tracheal cannulas in a temperature-controlled chamber. The heart has been cut away to expose the pulmonary venous return, which during perfusion drips into a funnel that serves as the bottom of the perfusion chamber. The lung is ventilated using positive pressure with 95% O2/5% CO2 at 56 breaths/min, with a tidal volume of 5.0 ml and end-expiratory pressure of 2 cm of water. Artificial perfusate (Krebs Ringer bicarbonate buffer containing 5 mM glucose and 4.5% bovine serum albumin, pH 7.4 at 37°C) was pumped through the lung via the pulmonary artery at a rate of 10 ml/min, and venous effluent was collected in 40-s fractions in a fraction collector directly below the perfusion chamber. A double three-way valve in the perfusion system was used to perfuse the lung with perfusate from either of two reservoirs that contained drug-free perfusate or the drug combination being studied. The accumulation of fentanyl in the lung was monitored by the appearance of tritium...
CALCULATIONS

Total uptake of fentanyl during the first pass through the human lung was determined by comparison to the nonextractable 3 indicator ICG.15,16,21-23 The amount of dye or fentanyl per milliliter 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 and 2). The ICG curve represents the fraction of the injected dose per milliliter of arterial blood versus time for the case in which no extraction by the lung occurs. The difference in the area under the dye curve and the drug curve divided by the area under the dye curve is the fraction of injected drug that was extracted from the blood into the lung in the first pass. To calculate the area under the first pass curve, semilogarithmic plots of the linear descending part of the curve were extrapolated to determine the fraction of injected dose in the blood per

in the 40-s venous effluent fractions. To study the effect of propranolol, the IPL was preperfused with propranolol for 4 min and then coperefused with propranolol plus 3H-fentanyl. A 0.5-ml aliquot of each fraction was added to 5 ml of scintillation fluid (ACS®, Amersham Corp.), and the amount of radioactivity was determined on a Packard Model 4130 liquid scintillation spectrometer. The radiochemical purity of 3H-fentanyl was determined by thin layer chromatography using silica gel-G plates in a chloroform:methanol:acetic acid (19:1:1) system. A single peak at an Rf of 0.3 indicated greater than 99% purity.

ANALYTIC PROCEDURES

The concentration of ICG and fentanyl in whole human blood was determined spectrophotometrically and by radioimmunoassay, respectively, as previously described.19,20

FIG. 1. Fraction of injected dose of ICG (open circles) and fentanyl (closed squares) per milliliter of arterial blood versus time (seconds) after iv injection of the dye-drug bolus. Points denoted by + represent the extraction ratios (ER) for fentanyl with time. Data are from a patient in the group who received no propranolol. Differences in area under the ICG and fentanyl curves at 95% ICG recovery indicate 22.3% uptake of fentanyl during the first pass through the lung. Initial extraction ratio of fentanyl was 0.94, and the times of peak ICG and fentanyl concentrations were 19 and 24 s, respectively, after injection.

FIG. 2. Fraction of injected dose of ICG (open circles) and fentanyl (closed squares) per milliliter of arterial blood versus time (seconds) after iv injection of the dye-drug bolus. Points denoted by + represent the extraction ratios (ER) for fentanyl with time. Data are from a patient receiving 120 mg propranolol per day for a month. Difference in area under the ICG and fentanyl curves at 95% ICG recovery indicate 20.6% uptake of fentanyl during the first pass through the lung. Initial extraction ratio of fentanyl was 0.82, and the times of peak ICG and fentanyl concentrations were 19 and 28 s, respectively, after injection.
second had there been no recirculation. For comparative purposes, the percent of injected fentanyl taken up into the lung was calculated at the time when 95% of the injected ICG had passed through the lung as previously described. The instantaneous extraction ratio \( E_R \) represents the fraction of fentanyl in blood taken up into the lung at each time point and was calculated as previously described. The cardiac output was calculated from the area under the ICG curves. Student's \( t \) test was used for statistical comparisons, and \( P < 0.05 \) indicated statistical significance.

**Results**

The mean ± SE body weight, age, and cardiac output (CO) for the two groups of patients are shown in table 1 along with the range of these values for the patients studied. No significant differences were observed in these variables between the two groups of patients studied. Furthermore, there was no apparent correlation between CO and first pass uptake of fentanyl.

Figure 1 shows a typical first pass uptake curve in the human lung for fentanyl and figure 2 shows the first pass uptake of fentanyl in the lung of a patient receiving 120 mg/day of propranolol for 4 weeks prior to this experiment. Each figure represents the fraction of the injected dose of ICG and fentanyl per milliliter of arterial blood in the 1-s blood samples as a function of time after injection of the dye-fentanyl bolus. Comparison of the fractions of injected ICG and fentanyl recovered in arterial blood samples (fig. 1) demonstrated an extensive first pass uptake of fentanyl in the human lung as previously reported.

For the patient shown in figure 1, the data indicated 82.3% of the injected fentanyl was taken up by the lung during the first pass. For all seven patients in this group, first pass uptake of fentanyl ranged from 76% to 87% with a mean ± SE first pass uptake of 82.6% ± 1.4%. The extraction ratio \( E_R \) for fentanyl was high (90%) in the initial part of the first pass through the lung. The \( E_R \) decreased but remained positive during the remaining portion of the first pass (fig. 1). This \( E_R \) curve is typical of that for compounds that exhibit a flow-limited distribution into the lung tissue. Although net flux of fentanyl is into the lung, during the first pass the decrease in \( E_R \) and the slight delay in peak fentanyl blood concentration compared to that for the ICG (2.1 s, table 1) indicate diffusion of some of the accumulated fentanyl out of the lung back into blood.

In comparison to figure 1 (no propranolol), the fentanyl peak in figure 2 is much larger than when no propranolol was present, indicating a lower first pass uptake of fentanyl in the lung. In the patient data shown in figure 2, the first pass uptake of fentanyl was only 20.3% of the injected dose. If patients receiving all doses of propranolol (30–120 mg/day) are considered as a group, the mean ± SE for the first pass uptake of fentanyl was 52.8% ± 6.3% of the injected dose, which was significantly less \( (P < 0.001) \) than that in the control group (82.6% ± 1.4% uptake) who were receiving no other drugs prior to the experiment.

Figure 3 shows a plot of percent first pass uptake of fentanyl as a function of the daily dose of propranolol that the patients were receiving as part of their normal medication prior to elective surgery. The patients who received no propranolol are grouped rather tightly, and the scatter of the data on the patients receiving propranolol was greater. However, analysis of variance showed that linear regression line for these data had a slope significantly less than zero. Assuming that a cause-and-effect relationship is revealed by this correlation, a number of factors in the group of patients receiving propranolol could contribute to the variability. For example, patient compliance with the propranolol prescription and rates of propranolol metabolism in each patient are not known.
Measurement of plasma propranolol concentrations, which was not done, might help explain some of this observed variability.

The effect of propranolol in the pulmonary uptake of fentanyl was also investigated using the isolated perfused rat lung (IPL) preparation. A single pass infusion was used with the rat IPL and the accumulation of fentanyl in the lung with time could be observed during a period of infusion with a constant concentration of $^3$H fentanyl. The choice of fentanyl concentration for the 10-min constant infusion was somewhat arbitrary. Because of its high potency, the dose and therefore the resulting plasma concentration observed with fentanyl is much less than other narcotic analgesics. Therefore, we selected an infusion concentration of 0.5 nmol/ml, which is ten times lower than the lowest dose used in our previous studies.12–14 The concentration of propranolol was 2.5 nmol/ml and was selected simply because the iv dose ratio for these two drugs for a single bolus of either is about five.

Figure 4 shows the percent of the infused $^3$H-fentanyl in the venous effluent in each 40-s fraction during the fentanyl infusion with and without propranolol. Radiolabeled $^{125}$I-albumin was used as a nonextractable vascular indicator to determine the concentration versus time profile of a substance not taken up by the lung. This was necessary because diffusion, tubing volume between the three-way valve and the lung, the lung vascular space, and nonhomogenous flow in the lung and tubing result in dilution of the infused indicators, which is evident in the first few venous samples collected after the start of infusion. The amount of fentanyl taken up into the IPL is proportional to the difference in area under the fentanyl curves and the $^{125}$I albumin curve. As seen in figure 4, the percent of infused fentanyl in the venous effluent early in time after the start of infusion is low, indicating a high initial extraction by the rat IPL similar to the high initial extraction of fentanyl seen in the human lung (fig. 1). However, with the constant infusion experiments in the rat IPL, the uptake decreases with time (increased venous concentration) as the fentanyl accumulates in the lung tissue. By the end of the infusion period (10 min), the venous concentration of fentanyl is approaching a steady state. These same uptake characteristics have been observed with other basic lipophilic amines in the rat IPL.13,14

When the rat IPL was preperfused and coperfused with propranolol, the fraction of the infused fentanyl in the venous effluent was significantly greater than when no propranolol was present throughout most of the 10-min infusion, as shown in figure 4. This represents a decrease in the pulmonary uptake of fentanyl in the presence of propranolol.

**Discussion**

The present study demonstrates both in humans and in an isolated perfused rat lung preparation that propranolol can alter the pulmonary accumulation of fentanyl. Such competition for accumulation in the lung is consistent with what is presently known about the pulmonary accumulation of basic lipophilic amines.3–14 The fact that pulmonary accumulation is greatest for basic organic amines independent of pharmacologic or other chemical characteristics is consistent with a nonspecific interaction within the lung. Such accumulation could be viewed as a competition for partitioning between the
blood and lipophilic areas of the lung such as lipoproteins. For the studies reported here we selected patients receiving chronic propranolol therapy with the idea that if sufficient propranolol accumulated in the lung it could decrease the pulmonary uptake of a fentanyl bolus used for induction of anesthesia prior to surgery. Both of these basic drugs exhibit high first pass uptake in the human lung.** The fact that the first pass uptake of fentanyl was decreased in patients receiving propranolol suggests significant accumulation of propranolol in the human lung after chronic oral administration. This is consistent with the report of Geddes et al.** who found that the first pass uptake of propranolol was decreased in patients receiving chronic propranolol therapy.

The decreased first pass accumulation of the fentanyl observed in patients receiving chronic propranolol therapy represents a potential pharmacokinetic mechanism of a drug–drug interaction. From the data in figures 2 and 3 and table 1, in a patient receiving 120 mg of propranolol per day, the first pass uptake of fentanyl could be decreased from about 80% to 20% of the injected dose. This means that four times as much of the injected dose of fentanyl enters the systemic circulation immediately after iv injection. This represents the extreme case for our study; however, considering the mean first pass uptake (50%) in patients receiving all doses of propranolol (30–120 mg/day), the amount of the injected fentanyl entering the systemic circulation is still more than double that in patients not receiving propranolol.

During the first pass through the circulation other organ systems would be exposed to two to four times higher plasma levels of fentanyl in patients receiving propranolol. Work by Rothstein et al.** also provides an example of such an effect of propranolol. They determined the pulmonary uptake of the long-acting local anesthetic bupivacaine, which can cause severe cardiac and CNS toxicity. In their rabbit lung preparation first pass pulmonary uptake of bupivacaine was 81%. If propranolol was given 15 min prior to bupivacaine, first pass uptake of bupivacaine decreased significantly to 70%. This 10% decrease in the first pass uptake of bupivacaine results in a 50% increase in the amount of drug entering the systemic circulation immediately after bupivacaine injection. Considering the narrow therapeutic index for local anesthetics, they suggested that this could be of toxicologic significance. In this sense a protective role of the lung for drugs with high first pass pulmonary uptake would be decreased in the presence of a second basic lipophilic amine.

Beyond the first few recirculations after fentanyl injection, the effect of propranolol on both fentanyl pharmacokinetics and pharmacologic action is difficult to assess. It would be dependent in part on the rate at which the pulmonary pool of fentanyl diffused back out of the lung and into the circulation. Taeger et al. have estimated that in the first 10 min after injection 60% of the fentanyl accumulated in the lung during the first pass diffuses back out into the circulation.** Based on our studies only about 20% of the injected fentanyl (no propranolol pretreatment) enters the systemic circulation immediately after the first pass through the lung. Based on the work of Taeger et al.*** we estimate another 50% of the dose would enter the systemic circulation over the next 10 min with the remaining 30% diffusing out of the lung at some slower but unknown rate.

This same type of approximation can be applied to the patients receiving propranolol treatment, but it must be remembered that the pulmonary pool of accumulated fentanyl is much smaller due to competition for uptake with propranolol. In the propranolol-pretreated patients (120 mg/day) 80% of the fentanyl enters the systemic circulation immediately after injection, and based on the back diffusion estimate of Taeger et al.*** another 12% of the injected fentanyl would enter the circulation in the next 10 min. This means that by 10 min after injection 92% of the injected fentanyl has entered the systemic circulation in the propranolol-pretreated patients compared with 70% in the nonpropranolol-pretreated patients. From this one would predict about 25% higher concentrations of fentanyl in the propranolol-pretreated patients; however, more accurate measurements of the rate at which accumulated fentanyl diffuses back out of the lung are necessary before more precise pharmacokinetic estimates can be obtained. Another factor that could also sustain higher plasma concentrations of fentanyl is that propranolol could also compete with fentanyl uptake in other tissues; however, little insight into this possibility can be provided by the present study.

Another question that arises is whether the bolus dose of fentanyl as it first passes through the lung displaces previously accumulated propranolol from the lung resulting in a sudden pulse of propranolol. Some evidence for this type of situation is provided by the studies of Jorfeldt et al.** In patients receiving mepivacaine infusion followed by a bolus dose of lidocaine no change in the first pass uptake of lidocaine was observed; however, the arterial concentration of mepivacaine increased transiently after the injection of lidocaine. They suggested this reflected a displacement of mepivacaine from pulmonary binding sites common to both drugs. Kornhauser et al. reported a similar displacement phenomenon in that chlorpromazine and imipramine injections given after a propranolol bolus in the isolated perfused rabbit lung or the intact dog resulted in an immediate increase in plasma propranolol concentration.** In our studies it is unlikely that fentanyl resulted in a measurable displacement of propranolol from the lung because a very potent drug such as fentanyl is given in very low doses and in this study was in the subtherapeutic range (75 μg). After a
high chronic daily dose of propranolol, the total amount that could be displaced from the lung by this small amount of a second basic lipophilic amine (fentanyl) would not be measurable.

One aspect of our study design that should be noted is that the patient group not receiving propranolol may not be an appropriate control group. It must be remembered that the patients receiving propranolol were receiving this therapy for a reason, usually some degree of hypertension or ischemic heart disease. We cannot rule out that their medical condition itself results in some change in the pulmonary accumulation of fentanyl. However, the fact that propranolol decreased the pulmonary accumulation of fentanyl in the rat IPL preparation supports the idea of a competition of the two drugs for partitioning into the lung tissue that is responsible for the decrease in first pass uptake of fentanyl in the human lung.

In conclusion, chronic propranolol treatment appears to result in a pharmacokinetically significant drug–drug interaction with iv administered fentanyl at least during the first pass through the lung. Also, it is predicted that increased plasma concentration of fentanyl due to decreased first pass pulmonary uptake would persist for several minutes after fentanyl injection. The pharmacodynamic significance of this fentanyl–propranolol interaction must now be assessed.

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