First-pass pulmonary retention of sufentanil at three different background blood concentrations of the opioid

F. BOER, F. H. M. ENGBERS, J. G. BOVILL, A. G. L. BURM AND A. HAK

Summary
Using a double-indicator technique, we have studied, in 10 patients undergoing aorto-coronary bypass surgery, first-pass pulmonary retention of sufentanil. Pulmonary retention was studied at three pseudo steady-state background blood concentrations of 2.8 (0.66), 6.9 (1.2) and 15.9 (2.6) ng ml⁻¹, respectively, produced by a computer-controlled infusion. Mean first-pass pulmonary retentions at these concentrations were 68 (95% confidence intervals 62-73), 65 (60-70) and 60 (52-67)%, respectively. First-pass pulmonary retention of sufentanil was significantly lower at the highest background concentration compared with the lowest background concentration. First-pass pulmonary retention of sufentanil was partly saturable in the range of concentrations used for clinical purposes. 

Key words
Analgesics opioid, sufentanil. Pharmacokinetics, sufentanil. Lung, metabolic function.

The lung is capable of significant uptake, release and metabolism of both endogenous and exogenous substances [1-3]. In vitro, significant lung uptake has been observed for both neutral and weakly basic lipophilic drugs [4, 5]. In isolated perfused lung models, steady-state uptake of basic amines into the lungs was shown to consist of at least two processes, one saturable and the other non-saturable [6, 7]. A decrease in retention of basic amines with larger or repeated doses has been observed in vivo [8, 9]. These observations suggest that the transport mechanisms, binding sites, or both, of weakly basic drugs in the lungs are at least partially saturable. If one of the mechanisms involved in the pulmonary extraction, retention, or both, of a drug is saturable, so that less drug is retained at higher concentrations, then a relatively higher fraction of the dose will reach arterial blood if the drug dose is increased.

Basic lipophilic opioids such as fentanyl and sufentanil undergo significant first-pass retention in the lungs [10-12]. For these drugs it is possible that first-pass pulmonary retention decreases with increasing dose. The aim of this study was to investigate the saturability of the binding sites for sufentanil in the lungs. The pulmonary retention of sufentanil was studied at three different background blood concentrations of the drug using a double-indicator dilution technique.

Patients and methods
The study was approved by the local medical Ethics Committee and all patients gave informed consent. We studied patients undergoing elective aorto-coronary bypass surgery. Patients with unstable angina pectoris, poor left ventricular function (as assessed by preoperative angiography) with valvular abnormalities or pulmonary disease were excluded. In a first group of 10 patients, first-pass retention of sufentanil was studied in a fixed order at three increasing pseudo steady-state concentrations of increasing magnitude. Pseudo steady-state concentrations of sufentanil were maintained by computer-controlled infusion. In another group of five patients, we examined the stability of the blood concentrations during the computer-controlled infusion (control group).

Patients received lorazepam 3-5 mg orally, 90 min before arrival in the operating theatre. Patients who were receiving β adrenoceptor blocking drugs, calcium entry blocking drugs and nitrates continued these medications until the morning of surgery. In the operating theatre ECG electrodes were attached to a peripheral i.v. infusion was established. A pulse oximeter was attached for monitoring SpO₂. A catheter was placed under local anaesthesia into a radial artery. Before and during induction of anaesthesia and before starting the study, patients received Haemaccel 500 ml followed by a slowly running infusion of 2.5/0.45% glucose-saline as a carrier for the computer-controlled sufentanil infusion. After induction of anaesthesia a pulmonary artery catheter was inserted via the right internal jugular vein.

Anaesthesia was induced and maintained with sufentanil, administered by a computer-controlled infusion pump. The computer (Atari Portfolio, Okasaki, Japan) was interfaced to a syringe pump (Ohmeda 9000, Strector, UK) via a serial RS232 communication channel. The computer program, written in Pascal by one of the authors, was supplied with three-compartment pharmacokinetic data for sufentanil [13]. The computer-controlled infusion was used to rapidly achieve and maintain theoretical target plasma concentrations of sufentanil.

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induction, the target plasma concentration of sufentanil was 9 ng ml\(^{-1}\), to be achieved in 3 min. After the patient had lost consciousness, pancuronium 100 µg kg\(^{-1}\) was given for neuromuscular block and the trachea was intubated. The patients’ lungs were ventilated with an oxygen in air mixture (\(F_{\text{O}_2} = 0.5\)) by intermittent positive pressure ventilation using a Servo 900-C ventilator at a frequency of 12 b.p.m. Minute volume was adjusted to maintain an end-expiratory carbon dioxide concentration of 4.5–5.5 %.

After intubation, the target concentration of sufentanil was decreased to 4 ng ml\(^{-1}\). In our experience this concentration is adequate to maintain anaesthesia in the absence of surgery. When the required concentration was reached and the predicted concentrations in the second and third compartment were less than or equal to 40 ng ml\(^{-1}\), the first determination of first-pass pulmonary retention was performed. The target concentration was then increased to 8 ng ml\(^{-1}\) and pulmonary first-pass retention was again determined. Finally the target concentration was increased to 16 ng ml\(^{-1}\) and the process repeated.

For measurement of first-pass pulmonary retention, sufentanil and indocyanine green were injected via the right atrial port of the pulmonary artery catheter in 1 s, followed by a 10-s saline flush. For this purpose sufentanil 200 µg (4 ml), indocyanine green 50 mg (Cardio-green, BBL Microbiology Systems, Becton Dickinson) in 5 ml of solvent and 1 ml of autologous blood were mixed in a 10-ml syringe. One millilitre of this solution was placed in a glass tube for later determination of the exact concentrations of sufentanil and indocyanine green.

The remaining solution was divided into three aliquots of 3 ml each in 5-ml syringes. The syringes were weighed before and after injection to allow calculation of the exact volume injected. From the measured concentrations of sufentanil and indocyanine green in the administered solution and the injected volume, the injected doses were calculated. The solutions were administered when the required predicted steady-state plasma concentration had been stable for 5 min.

Two minutes before and 2 min after each experiment 2-ml arterial blood samples were obtained for measurement of arterial blood-gas tensions. Cardiac output was measured at random throughout the respiratory cycle in triplicate and the mean value of these three measurements (if they were within 15 % of each other) was taken as the cardiac output of that phase. Heart rate, mean arterial pressure and mean pulmonary artery pressure were recorded immediately before the bolus injection. Immediately after injection of the test solution, arterial blood samples were obtained at 1-s intervals for 60 s. Blood flowing spontaneously from the radial artery cannula was diverted via an extension tube to a modified fraction collector containing 60 sampling tubes. Each tube contained heparin 40 µl (5000 u. ml\(^{-1}\)). Individual tubes were exposed to the blood flow for 1 s. Blood sampling was continued until 60 s after the injection. From each sample, 0.2 ml was separated for measurement of indocyanine green concentration, which was performed within 1 h after the experiment. The remaining portion of the whole blood sample was stored at \(-20^\circ\)C for measurement of sufentanil concentration. After appropriate dilution, the concentration of indocyanine green was measured spectrophotographically at 805 nm. Concentrations of sufentanil were measured by a highly specific radioimmunoassay. The techniques for measurement of indocyanine green and sufentanil concentrations have been reported previously [12].

The detection limit of sufentanil in this study was 0.45 ng ml\(^{-1}\) and the coefficient of variation of spiked concentrations was 8.9–9.4 %.

The stability of the background concentrations during the computer-controlled infusion was studied in a separate group of five patients. These patients were studied using the same experimental procedure as during the pulmonary retention study, except that the patients did not receive the mixture of sufentanil and indocyanine green. Sufentanil concentrations were measured in every fifth 1-s sample.

**Calculations**

Extraction and retention were calculated as described by Geddes and colleagues [9] and Jorfeldt and colleagues [14]. The background concentrations of indocyanine green and sufentanil measured in the first samples after bolus injection but before the indocyanine green concentration was increased by bolus injection were used to calculate the mean background concentration of indocyanine green and sufentanil. This mean background concentration was subtracted from the measured indocyanine green and sufentanil concentrations measured at each sampling time. The indocyanine green concentration vs time curve was taken as the reference curve representing zero retention in the lungs. The curve was corrected for recirculation by log-linear extrapolation of the terminal part of the descending portion. The concentrations of ICG and opioid in each sample were divided by the administered dose yielding dose-corrected quantities (from now on termed fractions, \(F_{\text{ICG}}\) and \(F_{\text{opioid}}\) with dimension ml\(^{-1}\). These fractions were used for further calculation of extraction and retention.

For each sampling time extraction was calculated by assuming that any difference between the fraction of sufentanil and the fraction of indocyanine green resulted from retention of sufentanil in the lungs. Extraction was therefore calculated as:

\[
E_t = \left(1 - \frac{F_{\text{opioid}}}{F_{\text{ICG}}}\right) \times 100\%
\]

where \(F_{\text{opioid}}\) and \(F_{\text{ICG}}\) = respective fractions of sufentanil and indocyanine green at sampling time \(t\). Retention was calculated:

\[
R_t = \left(1 - \frac{\text{AUC}_{t,\text{opioid}}}{\text{AUC}_{t,\text{ICG}}}\right) \times 100\%
\]

where \(\text{AUC}_t\) = area under the fraction vs time curve at time \(t\). AUC was calculated by the linear trapezoidal rule. First-pass retention was defined as retention up to the time when 95 % of the total area under the indocyanine green curve was reached.
Recirculation of sufentanil was assumed to have occurred when recirculation of indocyanine green was observed. For patients in whom recirculation occurred before 95% of the AUC of indocyanine green was reached, extraction and retention would not have been calculated but this did not occur in any patient. Cardiac output was calculated from the area under the indocyanine green concentration–time curve corrected for recirculation and the dose of indocyanine green administered using the formula:

\[ CO = \frac{D_{ICG}}{AUC_{ICG}} \]

The concentrations of sufentanil measured in the control patients during the 1-min sampling period were used to calculate the accuracy and precision of the computer-controlled infusion, as described by Raemer and co-workers [15]. For each sample the performance error (PE) was calculated as

\[ PE = \left( \frac{C_M - C_T}{C_T} \right) \times 100 \]

where \( C_M \) = measured sufentanil blood concentration and \( C_T \) = target sufentanil blood concentration as predicted by the computer system. The bias of the system is expressed as the median performance error of all blood samples (MDPE). The absolute PE values of all samples were used to determine the median absolute performance error (MDAPE), which reflects the inaccuracy of the computer-controlled infusion system. In each patient the stability of the background concentrations during each 1-min period was expressed as the coefficient of variation for each concentration (low, medium and high).

Patient data were compared between groups using two-tailed, unpaired \( t \) tests and Fisher’s exact test. Experimental haemodynamic conditions, blood-gas tensions, sufentanil doses and pulmonary extraction and retention data were analysed using repeated measures analysis of variance, followed by the Newman–Keuls range test when applicable. \( P < 0.05 \) was considered statistically significant. Results are expressed as mean (SD) or mean (95% confidence interval of the mean).

**Results**

There were no significant differences between patients in the pulmonary retention study group and patients in the control group in weight, height and medications used before operation (table 1). In the pulmonary retention group, pulmonary retention was studied at three background concentrations, indicated in tables 2–4 as low, medium and high. Table 2 shows the haemodynamic data and arterial blood-gas values during computer-controlled infusion of sufentanil, assessed before injection of a mixture of indocyanine green and sufentanil for measurement of first-pass pulmonary retention. *Significant difference (\( P < 0.05 \)) compared with low concentration.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Retention group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>178 (8)</td>
<td>173 (14)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>82.8 (11.9)</td>
<td>82.7 (16.5)</td>
</tr>
<tr>
<td>Medications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \beta ) blockers</td>
<td>9/10</td>
<td>4/5</td>
</tr>
<tr>
<td>Nitrates</td>
<td>10/10</td>
<td>4/5</td>
</tr>
<tr>
<td>Calcium entry blockers</td>
<td>5/10</td>
<td>4/5</td>
</tr>
</tbody>
</table>

Table 1 Patient data (mean (SD) or number) of the two groups. In the retention group the uptake and retention of sufentanil was studied at different background concentrations of sufentanil, which were maintained by computer-controlled infusion. In the control group the stability of the pseudo steady-state background concentrations during computer-controlled infusion was studied.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Low</th>
<th>Medium</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemodynamics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate (beat min(^{-1}))</td>
<td>62 (16)</td>
<td>60 (14)*</td>
<td>57 (15)*</td>
</tr>
<tr>
<td>PCWP (mm Hg)</td>
<td>9 (2)</td>
<td>10 (2)</td>
<td>10 (2)</td>
</tr>
<tr>
<td>Cardiac output (litre min(^{-1})) measured by:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indicator dilution</td>
<td>5.19 (0.9)</td>
<td>5.17 (1.06)</td>
<td>5.13 (0.95)</td>
</tr>
<tr>
<td>indicator dilution</td>
<td>4.76 (0.91)</td>
<td>4.81 (1.11)</td>
<td>4.85 (1.10)</td>
</tr>
<tr>
<td>Blood-gas values</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.38 (0.01)</td>
<td>7.38 (0.02)</td>
<td>7.38 (0.02)</td>
</tr>
<tr>
<td>( P_{CO_2} ) (kPa)</td>
<td>5.7 (0.4)</td>
<td>5.7 (0.4)</td>
<td>5.7 (0.5)</td>
</tr>
</tbody>
</table>

Table 2 Mean (SD) haemodynamic data and arterial blood-gas values during computer-controlled infusion of sufentanil, assessed before injection of a mixture of indocyanine green and sufentanil for measurement of first-pass pulmonary retention.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Low</th>
<th>Medium</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICG dose (mg)</td>
<td>16.9 (1.6)</td>
<td>16.7 (1.6)</td>
<td>16.7 (1.6)</td>
</tr>
<tr>
<td>Sufentanil dose (( \mu )g)</td>
<td>65 (7)</td>
<td>65 (8)</td>
<td>65 (8)</td>
</tr>
<tr>
<td>Background concentration (( \mu )g litre(^{-1}))</td>
<td>2.8 (0.66)</td>
<td>6.9 (1.2)</td>
<td>15.9 (2.6)</td>
</tr>
</tbody>
</table>

Table 3 Mean (SD) indocyanine green (ICG) dose, opioid dose and cardiac output calculated from the indocyanine green concentration–time curve, peak extraction and first-pass retention for each background concentration.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Low</th>
<th>Medium</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak extraction (%)</td>
<td>89 (84–93)</td>
<td>87 (84–91)</td>
<td>88 (82–94)</td>
</tr>
<tr>
<td>First-pass retention (%)</td>
<td>68 (62–73)</td>
<td>65 (60–70)</td>
<td>60 (52–67)*</td>
</tr>
</tbody>
</table>

Table 4 Peak extraction and first-pass retention for each background concentration (mean (95% confidence interval)). *\( P < 0.05 \) between low and high concentrations.
Figure 1 First-pass pulmonary retention (percentage of the dose administered) of sufentanil after a fast bolus injection in 10 patients during three pseudo steady-state concentrations of the drug, maintained by computer-controlled infusion. Each patient is indicated by a symbol.

Figure 2 Individual sufentanil concentration–time curve for five patients in whom blood concentrations were maintained by computer-controlled infusion at target sufentanil concentrations of 4 (A), 8 (B) and 16 (C) ng ml⁻¹.

Discussion

We have shown that first-pass retention of sufentanil decreased when sufentanil background concentrations increased, but that peak extraction was not affected by increasing blood concentrations. At least partial saturability of first-pass retention was therefore demonstrated. However, the difference in first-pass pulmonary retention of sufentanil between the lowest and highest concentrations was small (8%) and probably of limited clinical relevance.

The saturability of lung binding sites for opioids has not been studied in vivo. Other basic amines which undergo significant first-pass retention and the saturability of the binding of these drugs has been shown both in vivo and in vitro. Bertler and co-workers [8] found that in pigs, first-pass pulmonary retention of lignocaine was 41% with a smaller dose (0.5 mg kg⁻¹) and 28% with a larger dose (2.0 mg kg⁻¹). Geddes and co-workers [9] studied pulmonary retention of propranolol in patients undergoing cardiac catheterization. When patients were not receiving propranolol as oral daily medication, first-pass retention was 75%, while in patients who used the drug regularly, first-pass retention was 32.6%. Saturability of uptake of the basic amines in the lungs has been studied in greater detail in isolated perfused lungs models. A decrease in lung uptake with higher concentrations of the test drug in the perfusate was shown for mescaline [16], imipramine [17], propranolol [18] and methadone [19].

Pulmonary extraction and retention of drugs are dependent on several underlying mechanisms. First, the drug must be removed from blood to pulmonary tissues, either by simple diffusion or transport mechanisms (facilitated or active energy-requiring transport). Second, the drug must be bound in
tissues, either by partitioning to lipoid structures or by binding to tissue proteins. As transport and binding proteins have a limited number of binding places, both transport and binding could exhibit at least partial saturability, depending on the degree of binding. Tissue binding alone cannot explain the pulmonary uptake of opioids and other basic lipophilic drugs, as in vitro binding is higher than that predicted from in vitro distribution dialysis in tissue homogenates [20]. Possibly the high binding of these drugs to liver, kidneys and lungs is explained by their accumulation in liposomes, which are abundantly present in these tissues, and this accumulation is at least partially saturable [21–23].

We assumed that with increasing steady-state concentrations the occupancy of transporting and binding proteins might decrease, thereby decreasing the extraction and retention of additional drug given as an additional bolus. In order to show this non-linear drug binding, most of the available protein binding places must be occupied. It is possible that a greater decrease in sufentanil retention would have occurred if higher background concentrations had been used. However, we felt that the concentrations used in this experiment were justified, as they are in the range encountered in clinical situations.

The pharmacokinetic data set used in the program of our computer-controlled infusion system was derived from ASA I and II patients undergoing general surgery, whereas we studied patients with ischaemic heart disease receiving various cardiac medications. In order to assess the reliability of the computer-controlled infusion system in our patients, we investigated a control group of similar patients given sufentanil using an identical scheme but without bolus injections. The predictive accuracy of the system was evaluated by calculating the bias (MDPE) and inaccuracy (MDAPE) in this control group. MDPE is a measure of the general over- and underestimation by the computer of the actual plasma concentrations of sufentanil, whereas MDAPE is a measure of scatter of the measured values around the predicted values. In general, the predicted drug concentrations are within ±30% of the predicted concentrations when using an appropriate pharmacokinetic data set [15, 24, 25]. The bias and inaccuracy of the system in our control group were −4.7% and 27.5%, respectively, which is within the bounds generally accepted for clinical use of these systems. However, in the context of our study, the stability of the blood concentrations of sufentanil during each 1-min experimental period is more important than the accuracy of the predicted concentrations. The range of coefficients of variation of blood concentrations of sufentanil for individual patients was narrow for the high background concentrations, but greater for the medium and low background concentrations. However, as may be seen from figure 2, in both of these latter cases the greater magnitude in the coefficient of variation could be attributed to two patients.

In the control group the stability of the background concentrations, as maintained by the computer-controlled infusion, was assessed by obtaining arterial blood samples. It could be argued that it would have been more appropriate to prove stability of pulmonary arterial blood concentrations. However, we felt that arterial concentrations, which are at the venous side of the lungs, are more relevant to the concentrations in lung tissues and therefore to occupancy of binding places. Also, we used arterial concentrations in the experimental part of the study. Finally, it would have been technically impossible to obtain pulmonary arterial blood samples at the frequency and speed required for measurement of stability of pulmonary arterial sufentanil blood concentrations. As the samples would have had to be taken via the pulmonary artery catheter with a relatively large deadspace, a sample and flush technique would have been required and the speed of this is also limited [26].

We have shown that a decrease in pulmonary retention of sufentanil during higher background concentrations of the drug was demonstrable even in the clinical concentration range, but the decrease was small and probably not clinically relevant. If an additional sufentanil bolus is given during constant-rate, computer-controlled infusion or during repeated bolus administration, a predictable increase in sufentanil blood concentrations occurs in the first minutes immediately after administration of the drug.

Acknowledgement
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References
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Pulmonary retention of sufentanil


