Drug handling by the lungs

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The lungs are pharmacologically active organs and affect the blood concentrations of drugs given intravenously. The lungs can take up, retain, metabolize and delay the release of many drugs and compounds. The ability of the lungs to remove endogenous compounds from the pulmonary arterial blood was recognized in the 1960s. Philpot noted that compounds with significant pulmonary uptake were basic amines with \( pK_a \) values >8. Although not limited to such compounds, pulmonary uptake is most relevant for drugs with these characteristics. Many of the drugs used in anaesthesia are basic amines, and the pulmonary uptake of anaesthetics has attracted the interest of anaesthetists. This review describes how the pharmacokinetic function of the lungs can be studied, which anaesthetics are taken up by the lungs, how the pharmacokinetic function of the lungs is affected and how this can be related to systemic pharmacokinetics. A further introduction to the pharmacokinetic function of the lungs is available in earlier reviews by Bend and colleagues, Bahkle, and Roerig and colleagues.

In describing pulmonary uptake, several terms are used. The expression ‘pulmonary uptake’ is reserved for the process of transfer of a drug from the blood into the lungs, regardless of subsequent metabolism or release back into the blood. ‘Extraction’ is often used as a synonym of ‘uptake’. The expression ‘first-pass uptake’ is reserved for the instantaneous extraction of a drug and indicates the dynamics of the uptake processes. Thus, ‘extraction’ refers to the rate and direction of the transfer of the drug to and from the lung tissue after a bolus injection during a study of first-pass retention. When release from the lungs occurs, the extraction becomes negative. ‘Retention’ is related to the injected dose, and is expressed as the percentage of the injected dose that remains in the lungs after a given time, for instance after the first-pass period. ‘Extraction’ and ‘retention’ are typically used when the lung uptake is studied using a double-indicator dilution technique. In isolated perfused lung studies, the expressions ‘accumulation’ and ‘persistence’ are used to describe lung uptake. ‘Accumulation’ is the percentage of the studied drug retained in the lungs once equilibrium conditions have been reached, while ‘persistence’ is the percentage remaining after the lungs have been washed with a drug-free perfusate. If the drug undergoes elimination in the lungs, this process is described as ‘removal’ or ‘clearance’. Clearance is expressed as a rate (ml min\(^{-1}\)) or a percentage decrease in the concentration in the systemic arterial blood in comparison with the concentration in the pulmonary arterial blood.

Methods of investigation

Lung uptake can be studied both in the laboratory and at the bedside. The methods of investigation fall into three groups: in vitro methods, perfused lung models and in vivo methods. Table 1 gives an overview of the techniques. We will consider only the techniques that are used clinically and in intact animals.

In intact animals or in patients, pulmonary uptake of drugs can be studied by measuring arteriovenous differences after i.v. injection or during infusion of the drug. For drugs that undergo significant metabolic clearance in the lungs, a concentration difference will be present between the arterial and venous sides of the pulmonary circulation during steady-state conditions. On the basis of these concentration differences, the pulmonary extraction ratio can be calculated as the fraction of the cardiac output completely cleared of the test drug. This approach has been used to examine the pulmonary clearance of dopamine after cardiopulmonary bypass in cardiac surgical patients. Measurement of pulmonary clearance rate requires pulmonary arterial blood sampling, which may be difficult in some situations (e.g. studies in volunteers).
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Based on transpulmonary concentration gradients, lung uptake may be studied using mass balance calculations based on the law of conservation of matter.\textsuperscript{109} Using the concentrations in the pulmonary artery and the aorta (or radial artery), both the net flux into the lungs and the mass balance can be calculated. The mass balance of a drug over time is the integral of organ blood flow and the arterial–venous concentration difference. By plotting the net flux to the lungs and the mass balance against time during and after drug administration, one can distinguish between distribution and elimination. It is relatively easy to obtain pulmonary arterial blood samples in humans, using a pulmonary artery catheter, and the blood flow through the lungs (equal to cardiac output) can be measured by thermodilution. The uptake of drugs in the lungs can be studied using this technique in patients.\textsuperscript{13} Unfortunately, the method has significant limitations, allowing only cautious interpretation of the results, and can be technically difficult as it requires very frequent sampling from the pulmonary arterial catheter.

Transpulmonary concentration differences can also be analysed using system dynamics analysis.\textsuperscript{13 111} This method has been used to describe the pulmonary uptake of alfentanil in pigs and the pulmonary uptake of sufentanil in patients.\textsuperscript{13} The method has received little attention because the method and the mathematical analysis required to determine the transfer function are both complex.

The above methods require pulmonary arterial or mixed venous blood samples, which are technically difficult to obtain in patients if frequent samples are needed. Pulmonary arterial sampling can be omitted if another agent, which does not undergo pulmonary extraction, is given at the same time. Usually, a dye is used (e.g. indocyanine green (ICG)), and this technique is the double-indicator dilution technique. It was first used for the study of lung uptake of drugs by Geddes and colleagues\textsuperscript{27} and by Jorfeldt and colleagues\textsuperscript{50} to study lung uptake of propranolol and lidocaine in humans. The test drug and a dye or indicator are injected together on the arterial side of the pulmonary circulation, usually into the right atrium. Injection is followed by frequent blood sampling on the venous side of the lungs, e.g. from the radial or femoral artery. The blood concentration–time curve of the indicator is the reference curve of no pulmonary uptake (Fig. 1). Because both the indicator and the test drug re-enter the pulmonary circulation after their passage through the systemic circulation, peaks from recirculation are typically observed in the descending portion of the concentration–time curves. Before the indicator concentration can be used to calculate extraction and retention, the curve must be corrected for this recirculation. By log linear extrapolation (usually log linear regression) an estimate is obtained of the indicator concentration–time curve beyond the point of recirculation (thin line in Fig. 1). The curve thus obtained is the primary curve. After dose correction, the primary curve of the indicator and the concentration–time curve of the test drug are used to calculate extraction and retention of the test drug. The double-indicator technique requires rapid sampling techniques (often sampling every 1–3 s). The method can only be applied for the first-pass period and does not indicate what happens to the test drug after this period. The method relies on the assumption of mono-exponential decay of the ICG concentration curve to construct the primary curve, and this assumption may, in some circumstances, not be valid.\textsuperscript{16}

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\textbf{Fig 1} The concentration–time curves of an indicator and a drug that undergoes lung uptake. The indicator curve shows a clear secondary peak attributable to recirculation of the dye. From the dye curve, a primary curve is reconstructed by log linear extrapolation of the descending part of the curve. The concentration–time curve of the drug undergoing lung uptake lags behind the dye curve. Drug concentrations are initially less than the dye concentrations, indicating lung uptake, and later are greater than dye concentrations, indicating release of the drug from the lungs. As a result of release, the retention decreases gradually to 5% after 30 s, the point where 95% of the area under the dye curve is reached, the first-pass retention point.
Times after the first-pass period can be studied if more advanced methods are used, using recirculatory models.\textsuperscript{55} 61 With this technique, the indocyanine green concentrations after the first-pass period are used to construct a recirculatory pharmacokinetic model with pulmonary and peripheral compartments connected in series. Once a complete model is obtained for the indicator, the drug undergoing lung uptake can be modelled to describe its pulmonary uptake. Because the drug undergoes uptake in lung tissues, it may be necessary to include a tissue compartment in the model.\textsuperscript{61} We will discuss this possibility later in the review. Compared with the classic double-indicator dilution technique, recirculatory modelling allows the study of lung uptake beyond the first pass period. Contrary to other methods (mass balance, systems analysis), with this method lung uptake can be modelled without the need for pulmonary arterial sampling.

Pulmonary uptake of individual drugs

Many drugs undergo pulmonary uptake, but we will only discuss agents used during anaesthesia (Table 2). Propranolol is included because the $\beta$-adrenoceptor antagonists are often used by the anaesthetist and are taken up after i.v. injection. They also affect pulmonary uptake of anaesthetics and could alter the pharmacokinetics of these compounds.

Lidocaine and other local anaesthetics

The earliest works on lung uptake were on local anaesthetics such as lidocaine. In one of the first studies, the lung uptake of lidocaine was studied in anaesthetized pigs. The first-pass pulmonary uptake was 41 and 28\% after injection of 0.5 and 2 mg kg$^{-1}$ respectively.\textsuperscript{8} After two consecutive boluses of lidocaine 0.5 mg kg$^{-1}$ given 10 min apart to healthy volunteers, the first-pass pulmonary retention was 60 and 55\% respectively.\textsuperscript{30} The uptake in the lungs can be modelled using recirculatory modelling techniques.\textsuperscript{55} Lidocaine has an apparent pulmonary tissue volume of 39 ml kg$^{-1}$ in dogs, nine times greater than that of antipyrine (4.5 ml kg$^{-1}$), which is an indicator for total body water. This shows that lidocaine binds extensively to the non-aqueous content of the lungs (lipids, proteins).

In isolated rat lungs, the accumulation of lidocaine has a bi-exponential pattern, indicating at least two compartments available for pulmonary accumulation of lidocaine.\textsuperscript{83} At clinical concentrations, uptake of lidocaine by the lung appears to be linear.\textsuperscript{30} in vivo isolated perfused lung lobes from dogs, lung uptake was not affected by varying the concentration between 5 and 70 $\mu$g ml$^{-1}$. Lung uptake decreased with time from 41–51% in the first minute to 7–12% in the tenth minute, suggesting equilibration for a given constant blood concentration.

Several factors affect lung uptake of lidocaine. Lung uptake increases with pH, both in vivo and in vitro.\textsuperscript{85} 86 Because at greater pH more of the drug is in its base form, it seems that lung uptake increases because more is in the non-ionized, more lipophilic base form. Lung uptake is not affected by hypoxia\textsuperscript{30} or lung insufficiency.\textsuperscript{51} Lung uptake may be reduced by some drugs undergoing lung uptake, such as propranolol,\textsuperscript{71} but other drugs, such as mepivacaine,\textsuperscript{51} have no effect on lidocaine lung uptake.

Lidocaine can displace nortriptyline from the lungs,\textsuperscript{87} and increases the pulmonary uptake of propranolol.\textsuperscript{78} Lung uptake probably does not involve metabolism, as lidocaine accumulated without significant metabolism in rat lung slices.\textsuperscript{84}

The pulmonary uptake of other local anaesthetics is less extensive than that of lidocaine. Animal work found limited pulmonary uptake of bupivacaine. Irestedt and colleagues\textsuperscript{52} did not find first-pass pulmonary uptake of bupivacaine in dogs. In isolated rat lungs, the first-pass retention of bupivacaine, measured by a double-indicator dilution technique, was small (6–7\%), despite an initial peak extraction of 81–91\%.\textsuperscript{74} Others have shown extensive pulmonary uptake (first-pass retention up to 81\%) in the lungs of rabbits.\textsuperscript{97} 102 There could be significant differences between species in the pulmonary uptake of bupivacaine. In humans, lung uptake of the generally used local anaesthetics may be greater, depending on the particular local anaesthetic. Kietzmann and colleagues\textsuperscript{52} studied the pulmonary kinetics of prilocaine, mepivacaine and bupivacaine after a single epidural injection, using transpulmonary concentration gradients for the calculation of the pulmonary extraction ratio beyond the period of first pass. Two minutes after injection, the local anaesthetics were distinctly extracted by the lung (prilocaine 40\%, mepivacaine 20\% and bupivacaine 12\%). The lungs retained prilocaine more effectively than bupivacaine and mepivacaine. However, a transpulmonary concentration gradient was present for up to 15 min. After 8–30 min the extraction ratio became negative, indicating release of the local anaesthetics from the lungs.

Pulmonary uptake of bupivacaine is influenced by several factors. In rabbit lungs, a decrease in the acidity of the blood (pH 7.0–7.1) reduced pulmonary extraction and caused a 50% increase in the median peak bupivacaine concentration in the effluent blood after bolus injection.\textsuperscript{74} Pulmonary uptake of bupivacaine decreases with increasing dose.

| Table 2 | Drugs used in anaesthesia that can be taken up by the lungs |
|-----------------------------------------------|
| **Local anaesthetics**                       | **Opioids**                          |
| Lidocaine                                      | Fentanyl\textsuperscript{7} 67 94 106 113–115 |
| Bupivacaine\textsuperscript{52}               | Sufentanil\textsuperscript{11–14}   |
| Mepivacaine\textsuperscript{51}               | Alfentanil\textsuperscript{21} 11 13 106 |
| Prilocaine\textsuperscript{52}                | Pethidine\textsuperscript{90} 94     |
| **Anaesthetics**                              | Methadone\textsuperscript{90}       |
| Propofol\textsuperscript{12} 61 67 68         | Morphone\textsuperscript{11} 94      |
| Thiopental\textsuperscript{14}                | **Codeine**                          |
| Ketamine\textsuperscript{55}                  | Catecholamines                      |
| Benzodiazepines                               | Norepinephrine\textsuperscript{35} 40 64 |
| Diazepam\textsuperscript{54} 90               | Dopamine\textsuperscript{17} 18 98 103 108 |
|                                              | $\beta$-Adrenoceptor blockers        |
|                                              | Propranolol\textsuperscript{22} 38 39 45 60 75–77 |

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repeated administration and pretreatment with propranolol. Pulmonary metabolism of bupivacaine appears to be very small.

The pulmonary uptake of other local anaesthetics has not been studied as extensively as that of lidocaine or bupivacaine. In rat lung slices etidocaine accumulates considerably. In isolated rat lungs, prilocaine is substantially retained, particularly during the first pass. However, the ability of rat lung to degrade prilocaine was relatively small.

In patients given epidural injections, the transpulmonary concentration gradient of prilocaine in the first 2 min may be up to 40%. In these patients the transpulmonary gradient was only found during the first 15 min after injection, indicating that the buffering function of the lungs is limited and no significant pulmonary metabolic clearance occurs. The lungs are probably not sites of significant ropivacaine clearance either. Keeping constant arterial concentrations by continuous infusion in sheep showed no significant pulmonary clearance of ropivacaine. These findings support the general assumption that the lungs are only temporary sites of retention of local anaesthetics and that no metabolism occurs in the lungs (with the possible exception of prilocaine). The pulmonary uptake of local anaesthetics may be stereospecific. After i.v. injection, the concentration of L(+) mepivacaine in the lungs was more than twice that of D(-) mepivacaine. The pulmonary uptake of bupivacaine may not be stereoselective. Sharrock and colleagues found no significant differences in transpulmonary gradients of either the R(+) or S(-) enantiomers of bupivacaine as the extraction ratio was 10% in the first 5 min after epidural injection for both enantiomers. Stereospecificity of lung uptake could be because of differences in protein binding, transport processes or tissue binding.

Opioids
One of the first opioids to be studied for pulmonary uptake was morphine. In a perfused lung, approximately one-third of the morphine added to the system was taken up by the lungs by passive diffusion and non-specific binding to tissue anions. Morphine was not metabolized. In vivo, pulmonary uptake of morphine is very limited. Persson and colleagues studied the uptake and clearance of morphine by the lung in patients given morphine for postoperative analgesia. They found negligible extraction of morphine either during loading or in steady-state conditions. In patients before surgery the first-pass pulmonary retention of morphine, measured by indicator dilution, was similarly small (4–7%).

Meperidine shows significant first-pass pulmonary uptake in vivo. In patients given an injection of meperidine before surgery, maximum extraction was >90% and the first-pass pulmonary retention was 65%. During a two-stage infusion for postoperative analgesia, meperidine showed significant pulmonary uptake, with significant differences between venous and arterial concentrations. There was no pulmonary clearance of meperidine, as during steady state the central venous and arterial meperidine concentrations did not differ.

Animal studies show significant uptake and metabolism of methadone by the lung. After subcutaneous administration, the lung:serum ratio was between 25 and 60 in rats. Studies of rat lung slices suggest that transport to lung tissue is saturable and depends partly on simple diffusion. Similar observations were made in isolated perfused rabbit and rat lungs. When the lungs were perfused with methadone-free perfusate, the disappearance of accumulated methadone from the lung could be described by three disappearance rates, suggesting at least three pools of methadone accumulation. A small portion of methadone remained in the lungs after the washout period (non-effluxable pool) and another small portion was metabolized to mono- and di-N-demethylated metabolites. These animal studies suggest that pulmonary uptake of methadone could be clinically important, but we know of no clinical studies to support this.

The first-pass pulmonary uptake of fentanyl is great. After injection of a dose in surgical patients, the maximum extraction of fentanyl exceeded 90% and after the first pass 75% of the administered dose remained in the lungs. In another study, the first-pass retention was 43–87% and the disappearance from the lung after the first pass period was bi-exponential, with half lives of 0.22 and 5.78 min. Pulmonary uptake may be relevant during cardiopulmonary bypass for cardiac surgery. During and after cardiopulmonary bypass a transpulmonary concentration gradient is found, indicating that the lungs are temporary sites of fentanyl storage during bypass and that fentanyl is released from these sites after weaning from bypass. The high pulmonary uptake of fentanyl may be partly the result of an active uptake mechanism.

The first-pass retention of sufentanil (61%) in patients during coronary bypass surgery is similar to that of fentanyl. This phenomenon is partly saturable in the concentration range used clinically (2.8–15.9 μg ml⁻¹). If sufentanil is infused, a significant amount is retained in the lungs. If sufentanil 500 μg is given as a 10 min infusion, 49% of the dose is retained in the lungs at the end of infusion. After stopping the infusion, sufentanil is gradually released. After 20 min, 18% of the initial dose is retained in the lungs. The first-pass retention of sufentanil is not influenced by the mode of ventilation in anaesthetized patients undergoing mechanical ventilation.

The pulmonary uptake of alfentanil is less extensive. In one study the first-pass retention was 36–80% (median 59%) but in another study it was only 10%. Lung uptake of alfentanil is not affected by the mode of ventilation. In pigs the volume of distribution of alfentanil in the lung (and thus the extent of lung uptake) is not affected by large changes in cardiac output. In contrast to
fentanyl, the uptake of alfentanil is probably not active and this may explain the smaller pulmonary uptake of alfentanil.\textsuperscript{114}

**Induction agents**

The induction agents have not been studied as much as the local anaesthetics and the opioids. Thiopental has a first-pass retention of 14\% in man—less than diazepam, which has a first-pass retention of 30\%.\textsuperscript{93} Propofol may be taken up by the lung in both animals and humans in significant quantities. First-pass retention of propofol was 60–61\% in cats anaesthetized with pentobarbital and 39\% in cats also given halothane 1.5\%.\textsuperscript{68} The pulmonary uptake of propofol was decreased when the cats were pretreated with fentanyl 30 s before propofol administration.\textsuperscript{67} If fentanyl was given 3 or 10 min before propofol administration this inhibition of lung uptake did not occur. In sheep, propofol showed extensive pulmonary distribution and elimination clearance, but it was not clear whether the clearance was caused by metabolism or distribution to a deep tissue compartment.\textsuperscript{61} In patients, the first-pass pulmonary retention of a single dose of propofol is 28\%.\textsuperscript{32} When propofol was given as a continuous infusion, no significant transpulmonary concentration difference was seen after 2 min, suggesting that metabolism does not occur in humans. \textit{In vitro}, microsomal glucuronidation did not occur in rat, rabbit or human tissues,\textsuperscript{63} so the lungs are unlikely to be important sites of extrahepatic propofol metabolism.

Ketamine undergoes pulmonary extraction in dogs and the pulmonary tissue volume of distribution is twice that of antipyrine, a marker of the pulmonary extravascular water volume.\textsuperscript{36} The two enantiomers of ketamine do not show any difference in pulmonary distribution. There was no apparent pulmonary clearance in the dogs. In rabbits, the lungs may be sites of metabolic conversion of ketamine. In the supernatant of lung homogenates, ketamine is degraded to norketamine and possibly other metabolites.\textsuperscript{58} The kinetic parameters, however, showed that the lung enzyme systems involved in ketamine metabolism are more easily saturable than those in the liver. The clinical importance of this finding remains unclear.

**Muscle relaxants**

There is no substantial pulmonary first-pass uptake of rocuronium, vecuronium, rapacuronium or d-tubocurarine in pigs.\textsuperscript{5} Differences in pulmonary first-pass uptake do not contribute to the differences in potency and/or onset time among muscle relaxants, at least not in pigs.

**Catecholamines**

There is significant pulmonary clearance of dopamine and norepinephrine at clinical concentrations. In healthy patients, dopamine, at doses of 0.5, 1 and 2 µg kg\(^{-1}\) min\(^{-1}\), undergoes pulmonary extraction of 6, 12 and 12\% respectively.\textsuperscript{105} As the whole cardiac output flows to the lungs, the contribution to total plasma clearance of dopamine is higher than the pulmonary extraction, and is 4–20\% depending on the infusion rate. In critically ill patients receiving dopamine infusion, the extraction may be as great as 33\%.\textsuperscript{88} The contribution of the lungs to the total clearance of exogenous dopamine is not altered in patients after cardiopulmonary bypass.\textsuperscript{31}

Norepinephrine also undergoes pulmonary extraction. In relatively healthy patients the pulmonary extraction of exogenous norepinephrine is 3–16\%, similar to the extraction of endogenous norepinephrine.\textsuperscript{35} The lungs contribute on average 19\% to the whole-body clearance. If the pulmonary arterial concentrations of norepinephrine increase (from exercise or infusion), pulmonary extraction decreases.\textsuperscript{35} 64 66 Extraction or metabolism may not occur in patients with primary or secondary pulmonary hypertension.\textsuperscript{103} In dogs, pulmonary clearance was greater after cardiopulmonary bypass (35–42\%).\textsuperscript{35} 64 Despite this high pulmonary clearance, the arterial concentrations reached during infusion (0.2–0.6 µg kg\(^{-1}\) min\(^{-1}\)) were independent of the infusion site (central venous or left atrium).

**Propranolol**

The β-adrenoceptor antagonist propranolol was one of the first drugs studied for pulmonary uptake. Geddes and colleagues\textsuperscript{27} studied the first-pass uptake of \(^{14}\)C-propranolol using a double-indicator dilution technique in 10 patients undergoing cardiac catheterization. In seven patients who had not taken the drug previously, the mean first-pass retention was 70\%. In contrast, three patients taking regular oral treatment had a mean first-pass retention of 33\%, indicating that pulmonary uptake of propranolol is partially saturable. Lung uptake is less in severe emphysema, pulmonary hypertension\textsuperscript{76} and adult respiratory distress syndrome.\textsuperscript{69 75} In dogs the lung uptake of propofol increases from 53 to 64–81\% during anaesthesia, depending on the type of anaesthesia.\textsuperscript{77} Lung uptake is less during occlusion of a pulmonary artery and shock lung.\textsuperscript{75} In both anaesthetized and conscious sheep, the propranolol retained in the first pass after i.v. injection was partially recovered in lung lymph and in the fluid obtained by bronchoalveolar lavage.\textsuperscript{39}

In rats, the areas under the concentration curves were less when propranolol was injected i.v. compared with intraarterial injection.\textsuperscript{45} In rabbit lungs the removal of propranolol had a rapid (\(T_{1/2}=2\) min) and a slower (\(T_{1/2}=47\) min) distribution phase.\textsuperscript{53} Uptake of propranolol was less if the lungs were co-perfused with chlorpromazine. As chlorpromazine also inhibited the uptake of propranolol into isolated lung macrophages, it was assumed that lung macrophages are involved in the uptake of propranolol in the lungs. These findings were confirmed in rat lung slices.\textsuperscript{73}
Mechanisms of pulmonary uptake

The exact mechanism of uptake and binding of drugs to lung tissue has been fully characterized for only a few agents. The isolated perfused lung model is often used for this characterization, and the drugs used are largely non-anaesthetic. Most compounds appear to diffuse from the vascular space into the tissue, and bind to specific sites in the lungs. Some drugs are transported by specific endothelial transport mechanisms.

The mechanism for the steady-state uptake of basic amines into the lungs consists of two components, one saturable and one non-saturable. For most basic amines the saturable component reflects intracellular binding and facilitated diffusion, not carrier-mediated transport or metabolism. Washout studies in the isolated lung model have identified different pools of accumulative binding. Persistence of drug after the perfusion experiment is related to a slowly effluxing pool in the lung. After uptake, some drugs may be metabolized, but metabolism is insignificant for most drugs used in anaesthesia, except for some of the catecholamines.

The endothelial cell is probably the primary cell involved in the pulmonary uptake of drugs. It is the first cell encountered by blood-borne substrates. It is highly active metabolically and plays an important role in the breakdown of endogenous substrates. The endothelial cell may take up exogenous compounds that have structural similarities to an endogenous substrate, in terms of chemical groups and charge distribution. For some drugs, uptake into the endothelial cell may be facilitated by a carrier mechanism. The high pulmonary uptake of fentanyl may partly be the result of active uptake processes. In a flow-through system of pulmonary artery endothelial cells, fentanyl was partitioned into the cells 60 times more than the tissue-space water marker antipyrine. The fentanyl concentration in the endothelial cells was greater than would be expected if uptake occurred by diffusion alone, indicating that in vivo first-pass pulmonary uptake of fentanyl is largely attributable to vascular endothelial drug uptake by both a passive and a saturable active uptake process. The active uptake mechanism is specific, as alfentanil uptake into the endothelial cells is not facilitated. The active uptake of fentanyl is partially blocked by verapamil, a non-specific competitive inhibitor of drug transport. p-Glycoprotein, a glycoprotein that may play a role in the defence against xenobiotics and autacoids, is not involved in the transport of fentanyl. Apparently, the uptake of fentanyl is facilitated by a different, unknown mechanism.

Catecholamines are transported to the pulmonary endothelial cells by a transporter with the same properties as the neuronal norepinephrine transporter. Uptake is followed by metabolism by catechol O-methyltransferase and/or monoamine oxidase or efflux from the cell via the transporter mechanism.

After uptake of drug into the lungs, the drug may be bound in the tissue despite decreasing blood concentrations. In addition to binding to lipids, specific binding sites appear to exist for the basic amines. Basic amines are bound to phospholipids and may be associated with pulmonary phospholipidosis. They are also bound to mitochondria. There are at least two binding sites in the mitochondria, and accumulation depends on both lipophilicity of the amine and drug dose. The binding is competitively inhibited by other basic drugs but not by non-basic drugs.

Yet another important binding site for the basic amines are the lysosomes. Uptake in lysosomes is partly caused by so-called lysosomal trapping. Weak bases in their
un-ionized state permeate and accumulate in the acidic interior of lysosomes, where they are protonated and thus cannot diffuse back into the cytosol. The uptake of the basic amines into the lysosomes depends on the intralysosomal pH.43 There is strong competitive inhibition for lysosomal binding between the basic amines. 44

On the basis of extensive experiments, Yokagawa and colleagues119 have modelled the tissue distribution for basic drugs (Fig. 2). Basic drugs bind to non-lipophilic and lipophilic structures in the cells, but a significant portion of the drug enters the lysosomes via a pH-dependent mechanism. In the lysosomes the protonated drug binds to lipid structures in the liposomes (membranes etc.) by hydrophobic binding or aggregates. The model explains the interacting factors of lung uptake, in particular drug $pK_a$, lipophilicity and drug competition for binding to the lungs.

**Incorporating lung uptake of drugs into pharmacokinetic models**

Lung uptake of anesthetics affects arterial plasma concentrations after i.v. injection. Anesthetics could enter the lung when pulmonary arterial concentrations are high and are released from the pulmonary reservoirs once the concentrations have decreased later after injection. These effects will occur soon after giving the agent, when plasma concentrations differ in the various parts of the circulation, in the early mixing phase. This early mixing phase is difficult to express with the usual pharmacokinetic models.

A multicompartiment model is commonly used in pharmacokinetic modelling. The compartmental models assume that the injected drug mixes completely and instantaneously in the central compartment. The models are applied using samples taken some minutes after injection, when the mixing in the circulation is largely complete, and their use beyond the period of first pass has been widely established. By definition, the models are unsuitable for the mixing period, when the assumption of complete mixing is not met.

The mixing period may be better described with models that allow for recirculation and separation of the lungs from the rest of the circulation. Physiological models meet these requirements, containing compartments representing organs and tissues in the body. Each compartment is defined in terms of volume, blood flow, and apparent tissue–blood partition coefficients. These values can be determined in small animals and then scaled up to humans. Physiological models are used to describe the pharmacokinetics of i.v. drugs and inhaled agents. The model may be adapted by grouping tissues according to their significance to the pharmacokinetic and pharmacodynamic role. Physiological models have a great drawback: to determine a complete model, a large number of values have to be determined, and these may be
difficult to obtain. Recirculatory models are an alternative to compartmental and physiological models. Henthorn and colleagues introduced recirculatory models for the description of drug kinetics. Their model allows uptake in a central or heart–lung circuit and into two parallel peripheral compartments (Fig. 3). The model can be used to describe the kinetics of several drugs and indicators, and the effect of lung uptake of lidocaine, propofol and alfentanil. The uptake in the lungs can be characterized by volume of distribution of the distributive lung compartment (Fig. 3b).

Physiological and recirculatory models can be applied to the early mixing period after injection of drugs and can describe the presystemic effects of lung uptake.

Conclusions

The handling of drugs by the lungs is important for the anaesthetist, because most of the drugs that are used during anaesthesia undergo lung uptake to some extent. This is particularly important if the uptake is unexpectedly high or low. This was shown by Bokesch and colleagues, who studied the effects of intracardiac shunts on lidocaine pharmacokinetics in sheep. They created a surgical right-to-left shunt by connecting the pulmonary artery to the left atrial appendage in 1- to 2-month-old lambs, to achieve arterial oxygen saturations of 65–75%. After injection of lidocaine 1 mg kg−1, the peak arterial lidocaine concentration was 37 μg ml−1 in shunted animals compared with 21 μg ml−1 in normal control animals. In awake animals, the dose of lidocaine required to induce convulsions in the presence of a shunt was 4.7 mg kg−1 compared with 7.4 mg kg−1 in control animals. This illustrates that the lungs can protect against the effects of accidental injection of local anaesthetics. The loss of the buffering effect of the lungs after (accidental) bolus injection could be relevant in patients with moderate to severe right-to-left shunts and could make them more sensitive to adverse effects. Preoperative treatments such as β-adrenoceptor antagonists and anti-depressants may also reduce the buffering effect of the lungs, cause greater arterial concentrations after drug injection, and accentuate side-effects. There are many other factors that modify the buffering function of the lungs (Table 2), but they have not been studied extensively in patients and should be studied in clinical trials.

References


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