Arterial Paclitaxel Distribution and Deposition

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Abstract—Successful implementation of local arterial drug delivery requires transmural distribution of drug. The physicochemical properties of the applied compound, which govern its transport and tissue binding, become as important as the mode of delivery. Hydrophilic compounds distribute freely but are cleared rapidly. Hydrophobic drugs, insoluble in aqueous solutions, bind to fixed tissue elements, potentially prolonging tissue residence and biological effect. Paclitaxel is such a hydrophobic compound, with tremendous therapeutic potential against proliferative vascular disease. We hypothesized that the recent favorable preclinical data with this compound may derive in part from preferential tissue binding as a result of unique physicochemical properties. The arterial transport of paclitaxel was quantified through application ex vivo and measurement of the subsequent transmural distribution. Arterial paclitaxel deposition at equilibrium varied across the arterial wall and was everywhere greater in concentration than in the applied drug source. Permeation into the wall increased with time, from 15 minutes to 4 hours, and varied with the origin of delivery. In contrast to hydrophilic compounds, the concentration in tissue exceeds the applied concentration and the rate of transport was markedly slower. Furthermore, endovascular and perivascular paclitaxel application led to markedly differential deposition across the blood vessel wall. These data suggest that paclitaxel interacts with arterial tissue elements as it moves under the forces of diffusion and convection and can establish substantial partitioning and spatial gradients across the tissue. The complexity of paclitaxel pharmacokinetics requires in-depth investigation if this drug is to reach its full clinical potential in proliferative vascular diseases. **(*Circ Res*. 2000;86:879-884.)**

Key Words: paclitaxel ■ local drug delivery ■ artery ■ pharmacokinetics ■ polymeric drug delivery

Local drug delivery to the arterial wall can be achieved either through catheter-mediated endovascular application or through surgically implanted perivascular release devices.[1–3] Regardless of the interventional approach, the transfer of drug from a point of release to a target tissue relies on mechanisms of drug transport and binding such as diffusion, convection, and partitioning in and around target tissues.[4–8] These mechanisms are heavily dependent on the physicochemical properties of the drug and the surrounding environment. For example, hydrophobicity or absolute charge can regulate transport and distribution of drug in and around arterial tissues. Water-soluble drugs readily permeate into tissues,[9] and yet, the very processes that enable rapid equilibration and distribution also lead to rapid clearance.[5,10] As a result, there is increasing interest in less soluble, more hydrophobic compounds. Hydrophobic compounds are relatively insoluble in the aqueous phase, and tissue partitioning and retention are achieved by binding to available hydrophobic elements on fixed tissue sites.[9] Unlike hydrophilic drugs, hydrophobic compounds can possibly remain in and around target arterial tissues for some time after application. Whereas the diffusive and convective forces that drive these drugs across the blood vessel might adequately describe the fate of hydrophilic compounds,[4,11] hydrophobic compounds may be subject to associative and dissociative events that evolve over time with fixed arterial elements, resulting in localization of drug in proximity to the delivery source. The complexity of the forces that govern the coupled transport and binding of hydrophobic drugs requires in-depth characterization before they might fully be used to achieve clinical goals.

Paclitaxel is such a hydrophobic compound with tremendous potential in proliferative vascular diseases,[12–17] and its ultimate clinical use may depend on thorough characterization of these mechanisms.[12–14,18] We hypothesized that the hydrophobic nature of paclitaxel would drastically alter its transport properties through the arterial parenchyma from that of hydrophilic vasoactive compounds, such as heparin. Furthermore, we hypothesized that hydrophobic interactions between paclitaxel and the arterial wall would result in differential drug distribution patterns dependent on the aspect of drug application. We tested these hypotheses by quantifying the transport of paclitaxel within arterial tissues in an ex vivo preparation that allowed application to either the inner endovascular surface or the outer perivascular aspect of the artery in the presence of a controlled physiological transmural pressure gradient.

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Materials and Methods

Equilibrium Deposition

We defined the affinities of different tissues within the arterial wall for paclitaxel by measuring drug distribution at equilibrium. Calf common carotid arteries were harvested and transported in PBS with physiological calcium and magnesium (PBS^{++}, 0.01 mol/L $CaCl_2$ and 0.01 mol/L $MgCl_2$, Sigma) at 0°C. Arteries were opened longitudinally, cut into segments (190 to 260 mg), and placed in centrifuge tubes with 1.2 mL of [^{3}H]paclitaxel (2.11 mCi/mg, dissolved in 100% ethanol, Amersham Life Sciences) in Krebs-Henseleit (KH) buffer (0.017, 0.024, 0.034, 0.065, 0.07, 0.086, and 0.195 mg/L) at 4°C for 72 hours. Preliminary data showed that paclitaxel uptake reaches equilibrium in these arteries in <72 hours (not shown). After incubation, 0.100-mL samples of the bulk fluid around each artery were removed and assayed for [^{3}H]paclitaxel content through liquid scintillation spectroscopy (2500 TR Liquid Scintillation Analyzer, Packard-Canberra).

Transmural Distribution

Transmural arterial paclitaxel distribution was measured at each concentration through en face cryosectioning in which the arterial segments were sectioned parallel to the intima with a refrigerated microtome (Cryotome SME, Shandon, Inc).[19–21] Segment length and width were measured with a caliper, 0.020-mm thick sections were cut parallel to the intima, and the [^{3}H]paclitaxel content of each sample was determined by liquid scintillation spectroscopy. Tissue concentration at each transmural location was calculated as the mass of paclitaxel normalized by the measured tissue area and slice thickness.

Ex Vivo Perfusion

Calf carotid arteries were perfused ex vivo in an apparatus that simulated plasma flow and permitted examination of paclitaxel distribution when applied endovascularly or perivascularly.[4,11] The in vitro perfusion apparatus allows perfusate from an upper reservoir to flow through 3 arteries in parallel before emptying into a lower reservoir. The transmural pressure gradient was set by the relative height, hydrostatic head (ΔH), of the upper reservoir. Three arteries were immersed in a perivascular bath of KH buffer that was stirred and maintained at 37°C. Arterial paclitaxel distribution with endovascular or perivascular application of drug in KH buffer was examined after 15 minutes, 1 hour, or 4 hours. The height of the upper reservoir (ΔH) was adjusted to 1200 mm, inducing a physiological transmural pressure differential (ΔP) of 12 kPa (90 mm Hg). At regular intervals, 0.100 mL was removed from the perivascular and endovascular compartments for determination of [^{3}H]paclitaxel concentrations through liquid scintillation spectroscopy.

After each experiment, the artery between the cannulated ends was divided in 2, with 1 segment used for morphometric analysis and the remaining segment sectioned parallel to the intima, as described above. Total artery deposition was calculated as the sum of drug concentrations in all serial transmural sections normalized by the driving endovascular or perivascular concentration. Average artery deposition was calculated as the total drug deposition normalized by the total arterial volume. These values were compared using a Student t test in which $P<0.05$ indicated significant differences.

An expanded Materials and Methods section is available online at http://www.circresaha.org.

Results

Equilibrium Tissue Incubation

Arterial samples were incubated in [^{3}H]paclitaxel with KH buffer at several bulk concentrations (0.017 to 0.195 mg/L) for 72 hours at 4°C and sectioned en face to determine the equilibrium paclitaxel distribution. Partitioning (κ), defined as the tissue concentration (c_T) at equilibrium normalized by the bulk concentration (c_{Bulk}), was determined at every location for each artery, as follows:

$$\kappa(x) = c_T(x)/c_{Bulk} \quad (1)$$

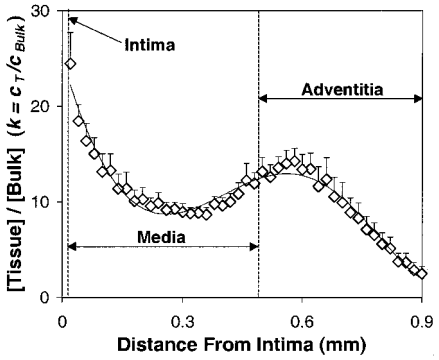

Figure 1. Equilibrium distribution of paclitaxel reveals partitioning above and beyond perfusate concentration and a spatial gradient of drug across the arterial wall. Seven tissue samples were incubated for sufficient time to reach equilibrium (72 hours) in buffered [^{3}H]paclitaxel solutions at various concentrations (0.017, 0.024, 0.034, 0.065, 0.07, 0.086, and 0.195 g/L). Cryotome sectioning (0.020 mm) enabled correlation of drug levels with position and revealed local maxima in the intima and adventitia (average±SE, n=7).

The partitioning at any transmural location was constant, regardless of the applied bulk phase concentration (Figure 1). At every transmural location, the tissue concentration of paclitaxel greatly exceeded the applied bulk concentration, indicating significant partitioning, which consistently varied with transmural location. By correlating the spatial distribution with histological arterial cross sections, we were able to ascribe the partitioning of paclitaxel to specific tissue elements within the arterial wall. Partitioning was maximal in the intima and declined precipitously within the most intimal regions of the arterial media to less than half the intimal level. At the outer edge of the media, ≈0.450 mm from the lumenal border, the paclitaxel partitioning increased gradually and peaked within the adventitia. The gradual decline in partitioning at the outer edge of the adventitia likely corresponds to the nonuniform radial thickness of this arterial layer seen on histological sections.

Endovascular and Perivascular Application

Arterial samples were perfused ex vivo for 15 minutes, 1 hour, or 4 hours with a physiological transmural pressure gradient. Paclitaxel was applied to the endovascular or perivascular aspect of the artery in KH buffer and drug distribution determined through en face cryosectioning. Because of slight variations in paclitaxel delivery concentration between experiments, tissue concentrations were normalized by the applied concentration. Paclitaxel distribution exhibited several common characteristics in all experiments conducted. Permeation distance into, and concentration of paclitaxel within, the artery increased with perfusion time for both endovascular (Figure 2A) and perivascular (Figure 2B) modes of delivery. Tissue concentrations were maximal nearest the intima with endovascular application and in the adventitia with perivascular application. The peak tissue

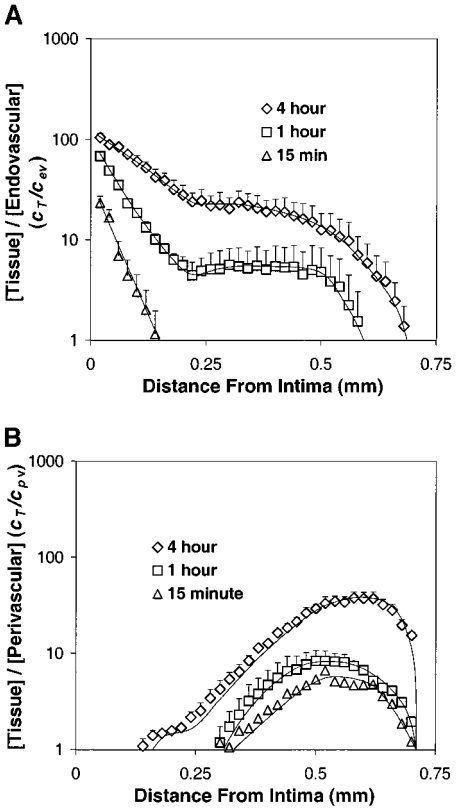

Figure 2. Tissue concentration normalized by the endovascularly (A) or perivascularly (B) applied concentration as a function of time in the presence of a physiological transmural hydrostatic pressure gradient of 90 mm Hg (average±SE, n=3). With the progression of time, drug was deposited more deeply into and to a greater extent within the blood vessel wall. Elevated drug concentrations were found in the intima and inner media after endovascular delivery and in the adventitia with perivascular delivery.

concentrations of paclitaxel offset from the perivascular delivery source are an artifact of the uneven, jagged anatomy of the adventitia. The distribution of paclitaxel at any location steadily increased with time as well.

During endovascular perfusion, paclitaxel was applied to the arterial wall from the lumenal aspect. Tissue concentrations in excess of 100-fold above perfusate concentration were observed (Figure 2A). Drug permeated ≈0.700 mm from the intima into the arterial wall after 4 hours of perfusion. Total artery deposition increased with each extension of the perfusion time (Figure 3). During perivascular perfusion, paclitaxel was applied to the arterial wall from the adventitial aspect. Maximum tissue concentrations 37-fold above perfusate concentrations were seen (Figure 2B). Drug permeated ≈0.580 mm from the outer adventitial border into the arterial parenchyma after 4 hours of perfusion, and again, the total tissue deposition increased as perfusion times were extended. Total arterial deposition with endovascular application was 2.9- and 2.0-fold higher than perivascular delivery at 1 and 4 hours, with $P=0.04$ and $P=0.02$, respectively. There was no significant difference in whole-artery deposition between perivascular and endovascular delivery at 15 minutes ($P>0.05$).

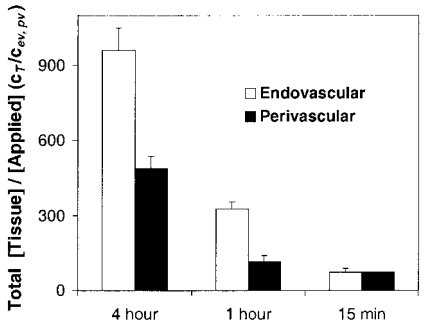

Figure 3. Total arterial deposition as a function of time in the presence of a physiological transmural hydrostatic pressure gradient of 90 mm Hg (average±SE, n=3). Total concentration was greater for endovascular delivery, but the transmural cryosectioning technique (Figure 2) reveals that different regions of the arterial wall are preferentially loaded by application to that site.

Effective Diffusivity Characterizes Arterial Transport

The effective diffusivity (D_{eff}) was estimated from the paclitaxel distribution data to facilitate comparison of transport of paclitaxel through arterial parenchyma with that of other vasoactive agents and to characterize the disparity between endovascular and perivascular application of drug.[19,22] This transport parameter describes the motion of drug in tissues given an applied concentration gradient and includes, in addition to diffusion, the impact of steric hindrance within the arterial interstitium; nonspecific binding to arterial elements; and, in the preparation used here, convective effects from the applied transmural pressure gradient. For each paclitaxel distribution profile (Figure 2), the permeation depth (l_p) was calculated and the effective diffusivity was estimated from the following:[19,22]

$$D_{eff}=l_p^2/6t, \quad (2)$$

where t is time. For perivascular delivery, because of the uneven anatomy of the adventitia, the permeation depth was calculated from the peak concentration, which was considered to correspond to the first transmural slice to contain a complete ring of adventitia. At all times, the effective diffusivity for endovascular delivery exceeded that of perivascular delivery (Table). These computations provide a quantitative measure for additional comparison of perivascular and endovascular application and allow us to contrast the

Effective Diffusivity Estimates From Paclitaxel Distribution Profiles and Equation 2 After Endovascular and Perivascular Application (10^{-6} mm^2/s, average±SE; n=3)

	Endovascular	Perivascular	Average
4 hours	4.87±1.49	2.66±0.03	3.76
1 hour	3.18±2.91	1.26±0.87	2.22
15 minutes	2.91±1.55	2.30±1.21	2.61

This measure includes, in addition to diffusion, the impact of steric hindrance within the arterial interstitium, nonspecific binding to arterial elements, and, in this preparation, convective effects from the applied transmural pressure gradient. The average at each time is also shown as an estimate of the effective diffusivity in the absence of convective effects (see text).

overall motion of the hydrophobic drug paclitaxel to prior measurements from hydrophilic compounds.

Discussion

Local delivery has special appeal for vascular diseases such as intimal hyperplasia, but it is rapidly becoming evident that drug potency is not the sole determinant of biological effect. For locally administered compounds to remain locally active, therapeutic drug concentrations at focal target sites must be created and sustained. Issues such as drug transport and binding in and around target tissues therefore become immensely important in local delivery and are to a great degree determined by drug-specific physicochemical properties. Hydrophobic drugs are relatively insoluble in the aqueous phase and bind to hydrophobic sites on fixed tissue elements. Association with tissue binding sites may impede the movement of drug across the arterial wall, localizing drug in arterial regions nearest the delivery source. We now demonstrate that the beneficial effects of paclitaxel at retarding post–vascular interventional intimal hyperplasia may stem in part from the physical properties of this compound and its interaction with tissue elements.

Paclitaxel Partitions Non-Uniformly Into Arteries

To characterize the affinity of different structures of the arterial wall for paclitaxel, we measured arterial drug distribution at equilibrium. Tissue concentration at all locations in the arterial wall greatly exceeded the applied bulk concentration ($\kappa \gg 1$, Figure 1), indicating that paclitaxel partitions, or binds to, elements throughout the blood vessel wall. Partitioning was greatest in the intima, followed by the adventitia and then the media, likely reflecting differential densities of nonspecific hydrophobic binding sites. Furthermore, although one might have anticipated a uniform distribution of paclitaxel across the media, there was a gradient in measured tissue paclitaxel and, by extrapolation, of hydrophobic binding sites, extending inward from both the intima and adventitia.

Kinetics of Arterial Paclitaxel Distribution

Arterial paclitaxel concentrations and permeation depth increased with time after both endovascular and perivascular application in KH buffer (Figure 2). In the absence of binding or cellular internalization, drug localization should be confined to interstitial void spaces, and one might expect tissue concentration to be less than the applied, surrounding bath concentration. Tissue paclitaxel concentration, however, greatly exceeded the driving endovascular or perivascular concentration, indicating that the vast majority of drug at any one instant is bound to fixed hydrophobic binding sites. The small minority of unbound drug in the void spaces is subject to transport by diffusive and convective mechanisms. Each drug molecule that diffuses down its concentration gradient, and simultaneously convects down the transmural interstitial pressure gradient, can bind to fixed arterial elements. In this manner, drug binding competes with forward motion and distribution. Drug molecules resume diffusive and convective motion only after dissociation from binding sites. Hydrophobic drugs such as paclitaxel heavily partition into tissues, and drug binding significantly slows transport, leading to large, localized concentrations adjacent to sites of application.

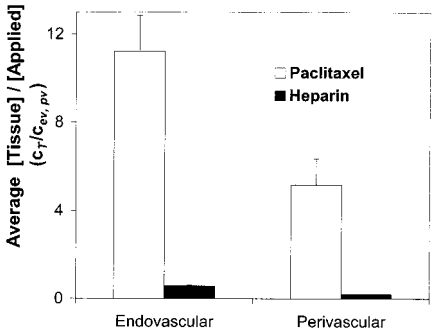

Figure 4. Comparison of paclitaxel and heparin average arterial tissue concentrations at 1 hour with delivery from the endovascular and perivascular aspects (average±SE, n=3).

The binding of hydrophobic drug to tissue elements is not instantaneous. The most intimal slice of arterial media should be in near-equilibrium with the applied endovascular source of drug. The tissue concentration nearest the intima, however, increased with time, indicating that partitioning evolves over hours (Figure 2A). The same phenomenon of slow progression to equilibrium occurs with tissue concentration peaks in the outer adventitia resulting from perivascular drug application. Clearly, drug binding and localization is not only a function of position within the arterial wall, but also a time-dependent process. Thus, the distribution of paclitaxel reflects a complex combination of transport and associative and dissociative events with nonhomogenous hydrophobic binding sites throughout the arterial parenchyma.

Transport and Localization of Hydrophobic Versus Hydrophilic Compounds

The important role hydrophobicity plays in transarterial transport is further demonstrated by comparing the average deposition of paclitaxel to that of a very hydrophilic molecule, heparin. The average normalized tissue concentration of paclitaxel 1 hour after perivascular and endovascular application is compared with that of heparin obtained from a prior study (Figure 4).[11] The average deposition for paclitaxel when compared with heparin is 19.4-fold higher after endovascular and 25.6-fold higher after perivascular application. This increased deposition is the result of the ability of paclitaxel to bind to many more nonspecific sites than heparin. This binding allows the tissue concentration of hydrophobic paclitaxel to exceed the applied concentration and indicates that the volume of distribution within arteries is very large. In contrast, the tissue levels of hydrophilic heparin cannot exceed that of the applied medium, and, as a result, its volume of distribution within arteries is low. Thus, the degree of hydrophobicity of a vasoactive drug affects the extent to which it can be loaded into arteries.

In addition to the maximal loading of tissues, the hydrophobicity of vasoactive drugs impacts the rate at which compounds move through tissues. In another previous study, we measured the diffusivity of heparin in the arterial media to be 7.73×10^{-6} mm^2/s.[4] The estimates of the effective diffusivity of paclitaxel in arteries ranged from 1.26×10^{-6} to

4.87×10^{-6} mm^2/s in the current study (Table). Note however, that the heparin diffusivity measured in the prior study was in the absence of a transmural pressure gradient, whereas in this study a physiological pressure gradient was always used.[4] At each ending time point, the effective diffusivity estimate from endovascular application exceeded that from perivascular application (Table), as the convective and diffusive forces are aligned in the former and opposed in the latter.[4,11] Thus, the effective diffusivities obtained from endovascular application are overestimates and those from perivascular delivery are underestimates. A reasonable measure of the effective diffusivities of paclitaxel in the absence of convective effects would be given by the average at each time (Table). Thus, the diffusivity of heparin in arterial tissues is more than double that of paclitaxel, despite the larger size of the heparin molecule. Heparin has an average molecular weight of ≈14 000, and in the absence of binding should move almost 6-fold more slowly through tissues than the much smaller paclitaxel (molecular weight 854).[23] The strong, nonspecific binding of the hydrophobic paclitaxel not only allows for larger concentrations to amass in tissues when compared with hydrophilic compounds, but also slows the transport of drug through the tissue as each molecule repeatedly binds and dissociates in the process of diffusing down its concentration gradient.

Perivascular Versus Endovascular Application

One of the fascinating aspects of paclitaxel distribution is that the total tissue deposition (Figure 3) did not adequately reflect the distribution of applied drug within the arterial wall (Figures 2A and 2B). Total tissue deposition was nearly 2-fold greater with endovascular than perivascular application (Figure 3). This may well reflect the synchronous effects of diffusive and convective forces when drug is released from the endovascular space, and their opposition with perivascular release. At the same time, however, the pattern of drug deposition varied significantly across the wall, and was itself dependent on the origin of drug administration (Figure 2). Whereas drug applied from the endovascular space was principally localized to the intima and inner media, perivascular release led to the highest concentrations within the adventitia. These findings may be of great clinical import. One might conclude endovascular application to be more efficacious as a result of the physical forces that augment drug transport through the arterial wall, for example, in the presence of convective forces that arise from physiological transmural pressure gradients. If the preferential distribution of drug is considered, such thinking may need to be revised. The spatial gradients in cellular and molecular effects after vascular injury direct or localize specific tissue reactions to particular vascular subcompartments and may require more tight regulation of drug transport to or from these areas. Endovascular delivery for events that are primarily adventitial may be as fruitless as the perivascular delivery that localizes drug to the adventitia when control of subendothelial phenomena is desired.

Paclitaxel Pharmacokinetics

Paclitaxel, derived from the bark of *Taxus brevifolia* (Pacific yew),[24] is a potent inhibitor of cell proliferation principally because of its action on microtubule formation.[25,26] As paclitaxel is poorly soluble in water (<0.01 mg/mL) and possesses no side groups that can be ionized in an acceptable pH range,[27] it has been suspended in vehicles for solubilization. Successful cancer therapy clinical trials administered paclitaxel suspended in 50% Cremophor EL (polyethoxylated castor oil surfactant) and 50% dehydrated alcohol (USP).[28–34] The same physicochemical properties that complicated systemic delivery of paclitaxel might improve retention of locally delivered drug. Paclitaxel inhibits vascular smooth muscle cell migration and proliferation, and it was proposed that this compound might play role in the prevention of vascular restenosis.[12,14] Local delivery devices[35–38] can place drugs in direct contact with target tissues, and yet studies utilizing these forms of paclitaxel delivery have exhibited mixed results. Porous balloon catheter delivery and coated stent release of paclitaxel decreased postangioplasty intimal hyperplasia in rat, rabbit, and porcine models.[13–17] Similar studies initially concluding prevention of neointima formation in rabbits after balloon angioplasty[12] were later shown to be statistically unfounded.[18] These studies clearly demonstrate that experimental results from any ex vivo or animal model must be considered in the context of the experiment in which they were obtained. Positive results for human in vivo studies with paclitaxel have yet to be conclusively demonstrated.

Discrepancies between animal model results and the absence of conclusive human in vivo studies compel examination of drug delivery issues. The disparate conclusions regarding the in vivo efficacy of paclitaxel might well be appreciated with an in-depth understanding of the physical forces that govern transport of this drug across the arterial wall. For example, in vivo evidence suggesting that the rate of release impacts the efficacy of paclitaxel[16] may also be explained by the rate of intra-arterial binding and subsequent region of deposition rather than an extra-arterial mechanism. By understanding the phenomena behind the transport of paclitaxel across the arterial wall, we may rationally and efficiently approach the local delivery dilemma and perhaps develop fundamental principles applicable to a wide array of local delivery scenarios.

Summary

The common understanding that paclitaxel is an insoluble compound is only a small part of its pharmacokinetic profile. Our data indicate that the interaction between this compound and the blood vessel wall, as governed by the physicochemical characteristics of the drug itself, impart unique transport qualities to this drug. Paclitaxel moves through arterial tissue subject to diffusive and convective forces, but binding to hydrophobic sites within arterial tissues dominates the localization and transport. Association with hydrophobic binding sites takes time to evolve and serves to impede forward movement of drug through the arterial wall. Perhaps as a byproduct of this impedance, the surface of the blood vessel from which drug delivery originates determines arterial distribution. Although we have used paclitaxel as a model hydrophobic compound, these illuminated principles and mechanisms should be applicable to other compounds pos-

sessing similar physicochemical properties and may ultimately help in the rational design and clinical utility of effective local drug delivery systems.

Acknowledgments

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