Pharmacokinetic Problems in Peritoneal Drug Administration: Tissue Penetration and Surface Exposure

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Both theory and clinical studies demonstrate that drug concentrations in the peritoneal cavity can greatly exceed concentrations in the plasma following intraperitoneal administration. This regional advantage has been associated with clinical activity, including surgically documented complete responses in ovarian cancer patients with persistent or recurrent disease following systemic therapy, and has produced a survival advantage in a recent phase III trial. Two pharmacokinetic problems appear to limit the effectiveness of intraperitoneal therapy: poor tumor penetration by the drug and incomplete irrigation of serosal surfaces by the drug-containing solution. We have examined these problems in the context of a very simple, spatially distributed model. If \( D \) is the diffusivity of the drug in a tissue adjacent to the peritoneal cavity and \( k \) is the rate constant for removal of the drug from the tissue by capillary blood, the model predicts that (for slowly reacting drugs) the characteristic penetration distance is \( (D/k)^{1/2} \) and the apparent permeability of the surface of a peritoneal structure is \( (Dk)^{1/2} \). The permeability-area product used in classical pharmacokinetic calculations for the peritoneal cavity as a whole is the sum of the products of the tissue-specific permeabilities and the relevant superficial surface areas. Since the model is mechanistic, it provides insight into the expected effect of procedures such as pharmacologic manipulation or physical mixing. We observe that large changes in tissue penetration may be difficult to achieve but that we have very little information on the transport characteristics within tumors in this setting or their response to vasoactive drugs. Enhanced mixing is likely to offer significant potential for improved therapy; however, procedures easily applicable to the clinical setting have not been adequately investigated and should be given high priority. Clinical studies indicate that an increase in irrigated area may be achieved in many patients by individualizing the dialysate volume and consideration of patient position. [J Natl Cancer Inst 1997;89:480-7]
in cm²), the familiar clearance-like term, cm³/minute, results. This “lumped” perspective has served us well for a number of purposes. It has provided quantitative predictability of PA from studies in experimental animals (6). It has enabled prediction of peritoneal and plasma concentrations and the resulting regional advantage to be expected in a clinical setting if the systemic pharmacokinetics are known (1). And it has provided a unifying paradigm for the description and analysis of numerous clinical and preclinical studies. The basic theory of regional drug administration now represents a mature technology that has been discussed in a variety of sources [e.g., (7,8)]. While the membrane property, PA, can be embedded in a physiologic model, and this model can be used to examine quantitatively effects such as first-pass drug clearance by the liver, the PA itself is purely empirical and uninformative concerning the mechanism of peritoneal fluid–tissue exchange or tissue penetration.

We have learned quite a lot about the rates, routes, and mechanisms of drug removal from the peritoneal cavity in the years since peritoneal drug administration was first proposed (9,10). In analyzing the problems of tissue penetration and serosal exposure for low-molecular-weight drugs (molecular mass up to about 6000 daltons), we have found that a very simple conceptual diagram of tissue adjacent to the peritoneal cavity. PA, the fluid in the peritoneal cavity at a concentration, Cₚ, can be defined from this equation (Fig. 2). This is the distance from the serosal surface at which the concentration difference between tissue and blood has

![Fig. 2. Conceptual diagram of tissue adjacent to the peritoneal cavity. Cₚ = the free drug concentration in the peritoneal fluid; Cₚ = the free drug concentration in the blood (or plasma). Solid line shows the exponential decrease in the free tissue interstitial concentration, Cᵣ, as the drug diffuses down the concentration gradient and is removed by loss to the blood perfusing the tissue. Also shown are the characteristic diffusion length, x₀, at which the concentration difference between the tissue and the blood has decreased to 37% of its maximum value, and xₐ, at which the difference has decreased to 5% of its maximum value [adapted from (6)].](Image 531x357 to 324x744)

If we solve the mathematical equation implied by this model at steady state, two very simple and useful results are obtained. First, the free drug concentration in the extracellular space of a tissue exposed to peritoneal fluid approaches that in the blood exponentially according to the formula

\[
C_e = C_B + (C_p - C_B) \exp \left[ -\frac{kD}{2}x \right],
\]

where x is the distance (cm) from the serosal surface.

A characteristic diffusion length, x₀, can be defined from this equation (Fig. 2). This is the distance from the serosal surface at which the concentration difference between tissue and blood has
decreased to 37% of its maximum value, which occurs at the surface

$$x_0 = (D/k)^{1/2}.$$  \[2\]

The distance from the serosal surface equal to $3x_0$ is a useful reference at which the concentration difference is 5% of the maximum value (Fig. 2).

The second result enables us to calculate the quantitative role of each tissue type in the absorption process. This calculation requires the definition of an effective permeability of the tissue structure shown in Fig. 2. As derived for the spatially distributed model (6),

$$P = (Dk)^{1/2}. \quad \text{[3]}$$

Fig. 3 illustrates how drug transfer from the peritoneal cavity to surrounding tissues occurs in a parallel fashion into individual tissues. The contribution of any tissue type to the overall transport can be determined by multiplying its permeability by the area, $A$, exposed to peritoneal fluid. For example, the contribution of the surface of the liver to transport would be $P_{\text{liver}}A_{\text{liver}}$. If the permeability and the area of each relevant tissue type are known, then these can be combined to provide an estimate of the overall permeability-area product, $PA$. Then

$$PA = \sum P_i A_i, \quad \text{[4]}$$

where the subscript $i$ designates each tissue, such as liver, stomach, diaphragm, small intestines, and anterior abdominal wall.

The spatially distributed pharmacokinetic model described above is obviously a great simplification of the actual anatomy and physiology. This is particularly true for tumors, which may exhibit spatial heterogeneity in both vascular density and tissue perfusion as well as transient blood flow in some vessels (12,13). The spatially distributed view of peritoneal transport, however, has some distinct advantages over the lumped approach. It is mechanistic and defines mass transfer in terms of more fundamental properties of tissues, such as the intratissue diffusivity, capillary permeability, capillary area per unit tissue volume, tissue perfusion, and surface area adjacent to the peritoneal cavity. This mechanistic approach links the theory to the large literature on microvascular physiology and transport through tissue. In principle, it is possible to predict the macroscopic properties such as $x_0$ and $P$ from equations 2 and 3 above. If data are inadequate to enable reliable prediction, the theory suggests experiments that can be conducted to obtain fundamental information. Furthermore, the functional form of the equations gives insight into the magnitude of changes in tissue penetration and rate of drug absorption that would be expected to result from pharmacologic or other manipulations. For example, a proposed vasoactive agent may decrease the blood flow and perfused capillary area. This would result in a decrease in $q$ and $a$, which would decrease $P$ but increase $x_0$. An increase in $x_0$ would favor penetration of drug into the tissue.

### Tissue Penetration

Both theoretical predictions and experimental measurements suggest very limited penetration of drugs into tissues, including tumors, adjacent to the peritoneal cavity. This limited penetration may limit antitumor effect, but it also may protect sensitive normal cells on the mucosal side of the gastrointestinal tract.

### Theoretical Predictions

We estimated that a hexose would reach 5% of its maximum concentration difference $[0.05(C_p - C_b)]$ at a depth of 459 μm in the jejunal capillary permeability of muscle. When the permeability of gastric capillaries was used, the 5% difference was estimated to be 265 μm (6). Calculations of the penetration of fluorouracil (5-FU) into the peritoneal tissue of the rat were complicated by extensive and nonlinear metabolism (14). At low concentration, the 5% level was estimated to be reached in about 160 μm, while this value was extended to about 650 μm at high concentrations that produced significant saturation of the drug metabolism in the tissue. A complex model suggested that the 5% concentration difference of $^{14}$C]EDTA would be reached in something of the order of 400-500 μm in the gastrointestinal tract of the rat (15).

### Experimental Measurements

The few reports of concentration profiles of low-molecular-weight chemicals in tissues adjacent to the peritoneal cavity result chiefly from studies in small animals. These studies are generally supportive of the very limited penetration suggested by theory. Polyethylene glycol-900 reached the 5% value at a distance of about 200 μm in rat jejunum, as shown by tissue sectioning (6). $^{14}$C]EDTA reached the 5% value at 430 μm, as demonstrated by quantitative autoradiography in gastrointestinal tissues of the rat (15). Los et al. (16) measured platinum concentrations in C531 colon adenocarcinoma growing intraperitoneally in the rat by proton-induced x-ray emission following intraperitoneal and intravenous administration of cisplatin. They

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Fig. 3. Illustration of how drug transfer from the peritoneal cavity into surrounding tissues can be divided into parallel paths governed by tissue-specific permeabilities, $P_i$, and areas, $A_i$, where the subscript $i$ can be $L$ for liver, $V$ for hollow viscera, and $P$ for parietal tissue. Low-molecular-weight drugs move from the peritoneal tissues into the rest of the body primarily via blood flow [adapted from (25)].
observed that the tumor concentration was significantly elevated by the intraperitoneal route at 1.0 mm from the periphery but not at 1.5 mm. These data are difficult to interpret because of the 168-hour delay between the last drug administration and tissue sampling. The results were confirmed in a similar study in tumor-bearing rats (17), in which the tumor concentration was observed to be significantly elevated 24 hours (single dose) or 48 hours (three injections) after the intraperitoneal route at a depth of 1 mm.

Related studies have been conducted by Wientjes and his co-workers on applying the penetration model to bladder and skin. There is significant resistance to transport offered by the urothelium and by the stratum corneum. To ensure that profiles were measured within perfused tissue, the subepithelial tissue of the bladder and the dermis of the skin were sectioned. The distance for a concentration decrease of 50% was reported to be about 500 μm for mitomycin C in both dog (18) and human (19) bladders, 500 μm for doxorubicin in human bladder (20), and 386 μm for 2′,3′-dideoxyinosine in rat dermis (11). The published values for the 50% decrease in bladder and skin suggest deeper penetration in these tissues than in the peritoneal tissues discussed above. In bladder, however, distention of the tissue was not accounted for. Relaxation and thickening of the tissue during its removal would be expected to flatten the gradient that had existed in vivo, so that the agreement between bladder and peritoneal tissues is probably better than the raw data would suggest.

**Exposure of Serosal Surface**

Various observations in experimental animals suggest limited exposure of the peritoneal surface under conditions of peritoneal dialysis. Adequate quantitative data are not available in human subjects, but the experimental studies predict a major problem. In fact, cancer patients may present additional problems because of their altered peritoneal anatomy with adhesions and posturgical scarring.

Simulated peritoneal dialysis experiments were carried out in anesthetized, supine rats with Evans’ blue dye and bovine serum albumin in the dialysis solution (21). Large parts of the visceral and parietal peritoneum displayed no stain or very little stain. These include one side of the cecum and stomach as well as portions of the small and large intestines and of the diaphragm. These results imply that much of the peritoneal surface has little or no contact with dialysis fluid during quiescent dialysis.

A number of studies of eviscerated animals (22-24) have reported relatively little reduction in the rate of clearance of low-molecular-weight substances from the peritoneal cavity, despite the removal of a large fraction of the peritoneal surface area. These observations, combined with theoretical calculations (25), led us to conclude (incorrectly) that the surface of the liver has a disproportionately large role in the absorption process. In an attempt to validate that conclusion, permeabilities of the rat liver, cecum, stomach, and abdominal wall were measured in vivo with a small diffusion chamber (21). The permeabilities were approximately $2 \times 10^{-3}$ cm/minute for mannitol across all tissues for both plasma-to-chamber and chamber-to-plasma transport. Furthermore, when the individual values of $P_a$, were multiplied by the superficial surface areas, $A_s$, of the rat tissues measured following dissection and the $P_a A_s$ products were added to obtain the overall $PA$ as shown in equation 4, the predicted value was three to four times the value determined in intact rats.

This discrepancy between the geometric peritoneal surface area and the effective functional surface area available for transport is supported by a study by Levitt et al. (26) of peritoneal transport of urea, creatinine, and L-glucose in the rat. The rats were placed on an orbital shaker; at a shaking rate of 250 min$^{-1}$, the $PA$ increased about fourfold from its stationary value, which is in good agreement with the discrepancy observed above. The loss of protein from the animal to the dialysis solution increased by only about 50%. This finding suggests that dialysis solution may have sufficient access to much or most of the surface to remove slowly diffusing proteins in the stationary animal but is not adequately mixed to remove rapidly diffusing compounds uniformly. Also, the stationary value of 0.34 mL/minute observed for L-glucose uptake was in good agreement with the value of 0.36 mL/minute observed for mannitol (21). Results analogous to those of Levitt et al. (26) have been presented recently by Rippe et al. (27).

**Approaches to Improving Drug Distribution**

**Tissue Penetration**

Obtaining large increases in the tissue penetration of low-molecular-weight drugs may be difficult. As shown in equation 2, the penetration distance is equal to the square root of the ratio of the intratissue diffusivity and the rate constant for drug removal from the tissue ($D/k$)$^{1/2}$. Increasing the penetration distance requires an increase in $D$ and/or a decrease in $k$. Because of the square-root relationship, the ratio $D/k$ would have to be quadrupled to produce a doubling of penetration. The tissue diffusivity is a function of the tissue structure and the drug properties; it is equal to the diffusivity in the interstitial space of the tissue (which incorporates the tortuous path that a molecule must traverse) and the volume fraction of tissue interstitial space. Introducing dialysis solution into the peritoneal cavity of rats and raising the intraperitoneal pressure from 0 to 4 cm H$_2$O cause the extracellular space of the anterior abdominal wall to double (Flessner MF: unpublished observations). This expansion of the interstitium likely increases the effective diffusivity; however, we are not aware of clinical data to substantiate these preliminary observations in rats or the validity of generalizing to tumor nodules on the peritoneum.

In principle, the value of $k$ can be reduced by pharmacologic measures, such as the administration of vasoactive agents. If we take $k$ to be of the form suggested by Gupta et al. (11), $k = paq/(pa + q)$, then a decrease in tumor blood flow would be expected to reduce $k$ through its effect on both $q$ and possibly the functional surface area, $a$, per cm$^3$ of tumor. There do not appear to be published studies of the effect of vasoactive agents on tissue penetration; however, there is a large literature on the determinants of tumor blood flow, as reviewed by Jain (13), and on blood flow manipulation for therapeutic purposes, as reviewed in a number of sources [e.g., (11,28,29)]. Most of the data are derived from a variety of experimental systems, and the results can be confusing and appear contradictory because of the complex interaction between normal and tumor vasculature, differing mechanisms of drug action, and varying responsiveness of
tumor and normal host vasculature. Extrapolation from one experimental system to another and to tumors in humans is problematic and could be misleading. The joint effects of vasoactive drugs and alterations in systemic blood pressure must be considered in predicting the effect of a particular procedure on transport within tumor.

In addition to vasoactive drugs, high systemic doses of glucose have been shown to produce large decreases in tumor blood flow in a variety of experimental preparations (30). While these doses are associated with significant hyperglycemia [e.g., (31)], the glucose concentrations are easily achieved in the peritoneal cavity during dialysis. It is possible that the choice of glucose-containing dialysate compared with saline or other solutions could affect tumor penetration through an effect on tumor perfusion. A therapeutic role for glucose has been hypothesized (32).

We are aware of no data on the effect of vasoactive agents on tumor growing on the human peritoneum. The tumor physiology clearly may be different for nodules that persist or recur following systemic chemotherapy compared with those remaining after surgery. There is a clear need to develop techniques for the study of tumor blood flow in a clinical setting.

Interest in the effect of vasoactive agents on the normal tissue would not be so much to increase penetration as to decrease the PA. As shown in equation 3, \( P = (Dk)^{1/2} \). A reduction in PA produces an increase in the regional advantage, so that a larger value of \( C_p \) can be tolerated at a fixed limiting systemic toxicity. Intraperitoneal dopamine decreased the rate of transfer of urea across the peritoneum in dogs by 34% accompanied by a small but statistically significant increase in blood pressure (33). Administration of vasopressin (antidiuretic hormone) to dogs produced a decrease in urea dialysance of 19% (34) and a decrease in the dialysance of potassium and iodide of 20% and 53%, respectively (35). A recent study (36) examined the effect of vasopressin on peritoneal drug absorption of fluorouracil, carboplatin, and etoposide in the pig. The vasopressin doubled the arterial blood pressure and increased the peritoneal fluid-to-plasma concentration ratio for carboplatin and etoposide but did not decrease the peritoneal clearance of any of the three drugs. The relative insensitivity of PA to pharmacologic manipulation is not surprising in view of the robustness of the distributed model. The theory predicts that the \( P_i \) for each tissue varies as the square root of the parameter \( k_j \) in that tissue. Thus, a 50% reduction in this rate constant would lead to only a 29% decrease in \( P \) and a concomitant increase of 41% in the penetration distance.

Perhaps counterintuitively, macromolecules may penetrate more deeply into some tissues than low-molecular-weight agents despite their low diffusivities. This statement is supported by concentration profiles of \(^{125}\text{I} \)-labeled human serum albumin in normal peritoneal tissues of the rat (37) and should not be generalized to tumors for the reasons discussed below. The apparent anomaly derives from the size selectivity of continuous capillaries (38) and the important role of convection in macromolecular transport. Capillary permeability decreases greatly to macromolecules of the size of albumin or larger so that removal of such proteins from tissue tends to occur through the lymphatic system. Diffusion of bovine serum albumin in normal and necrotic tissues in a rabbit ear chamber (39) and of albumin and nonspecific monoclonal antibody (immunoglobulin G) and Fab’ antibody fragment in a human tumor xenograft (40) did not show significant hindrance. This result may suggest that the ratio \( Dk \) could be higher for macromolecules than for low-molecular-weight drugs in tissues with continuous capillaries. Furthermore, movement of macromolecules in tissue can be dominated by convection (bulk flow) driven by hydrostatic pressure gradients rather than by diffusion. Pressure gradients in the peritoneal cavity have been measured only for the abdominal wall of the rat (41); we do not know what gradients exist in other tissues including tumors. Stelin and Rippe (42) calculated a fluid uptake rate of 1.25 mL/minute from human subjects in the absence of crystalloid osmotic gradients. Flesner and Schwab (43) showed that protein clearance in the rat was approximately equal to measured fluid loss when protein data were corrected for apparent binding. The 1.25-mL/minute clinical rate of fluid absorption is about an order of magnitude lower than PA values of typical low-molecular-weight drugs. A spatially distributed model with an average convection velocity corresponding to this fluid uptake rate suggests only a small effect on diffusive penetration of small molecules.

Two caveats must be attached to the idea of employing high-molecular-weight agents or high-molecular-weight carriers of other drugs for penetration of tumors attached to the peritoneal surface. First, the relatively immature neovascularature of tumors may not show the same size selectivity as normal continuous capillaries (44). Second, while we are aware of no measurements of interstitial pressure in tumors growing on serosal surfaces, elevated pressures have been observed in a number of other sites (45,46). There may be efflux of fluid from tumors. Butler et al. (47) obtained fluid loss from experimental mammary tumors in rats of about 2.3-3.7 \( \mu \text{L/minute per gram of tumor} \). If these values are similar to those from small tumor nodules on peritoneal surfaces, for which we have no data, then convection might reduce tumor penetration by low-molecular-weight pharmacologic agents and significantly retard penetration by macromolecules. Despite these caveats, macromolecular agents and carriers appear worthy of investigation in experimental systems.

A complete description of macromolecular transport, including the relative roles of convection and diffusion and the influence of tissue binding and metabolism, is beyond the scope of this review, which focuses on small molecules. Macromolecular transport is an area of active investigation. Some relevant preliminary data have been obtained on tissue concentration profiles of an immunoglobulin G (monoclonal antibody 96.5) in both normal tissues and human melanoma xenografts (FEMX-II) growing in the anterior abdominal wall of athymic rats (48,49).

Paclitaxel (Taxol) would be an interesting agent to investigate in the context of drug penetration (50,51). It has established activity against ovarian cancer. It shows long persistence in the peritoneal cavity; the peritoneal clearance is approximately 0.5 mL/minute in human subjects. The low peritoneal clearance, combined with a relatively large clearance in the body, results in a regional advantage in terms of the area-under-the-curve ratio in peritoneal fluid compared with plasma of about 1000. The peritoneal pharmacokinetics of paclitaxel are reminiscent of a protein rather than of a drug with its lower molecular weight. The reasons for this are not clear. Paclitaxel is not very soluble in
water or heptane. It is administered in a mixture of Cremophor EL (a polyoxyethylated castor oil) and ethanol (52), and its actual physical state in the peritoneal cavity is unknown. We speculate that it may be strongly bound to ascitic proteins or could possibly form a micellar suspension. Either of these states could greatly alter its pharmacokinetics in the peritoneal fluid. Whether the slow clearance from the peritoneal cavity is reflected in deeper tissue penetration is currently unknown but should be investigated in an experimental tumor model.

**Exposure of Serosal Surface**

If the surfaces of tumor nodules are not exposed to drug-containing solution or are inadequately exposed, then the rationale for regional administration is compromised and treatment failures could result. The instilled fluid volume is conventionally chosen to be an arbitrary value, typically 2 L. Keshaviah et al. (53) conducted a careful study of the effect of dialysate volume on the PA of urea, glucose, and creatinine in human subjects. They observed that the PA increased almost linearly from infused volumes of 500 mL to 2000 mL with the subjects in the sitting position. The values almost doubled over this range. Further volume increases to 3 L produced less than a 10% increase in the PA normalized to the 2-L fill volume; however, the volumes for the peak mass transfer rate were found to increase with body surface area of the patient. The authors concluded that the increase in PA reflected an increase in effective peritoneal surface area. Brandes et al. (54) observed that the PA was increased in the supine compared with the upright position for urea, creatinine, and glucose by 24%, 19%, and 17%, respectively. A study (55) published only in abstract form supported a linear increase in PA with intraperitoneal exchange volume as well as an effect of body surface area. In addition, a higher transfer coefficient was observed for urea in subjects in the supine position compared with conditions of ambulatory exchange (55). During peritoneal drug administration, it would appear prudent to optimize the volume in which drug is delivered for each patient and to consider patient position based on the above observations.

Physical approaches have been used to attempt to improve mass transfer during peritoneal dialysis. They include recirculating systems (56-58) and reciprocating systems (59,60). The data are difficult to interpret because solute clearances were reported and none of the references analyzed the effect of the procedure on the PA in the absence of confounding variables such as average dialysate flow rate and ultrafiltration.

Relevant clinical data were obtained by Miller et al. (56), who placed catheters in the left gutter and in the upper quadrant under the liver. They studied the effect of variations of a number of intermittent and recirculated dialysis techniques on the clearance of urea, creatinine, and uric acid. The most relevant comparison for the effect of mixing on clearance examined a single-pass technique in which dialysate flowed at a rate of 100 mL/minute with the same overall flow rate to which a recirculated flow of 100 mL/minute was added so the flow through the peritoneal cavity was 200 mL/minute. The clearances were unchanged by the addition of recirculation. We note that the clearances of urea and creatinine were much higher than the PAs obtained by Keshaviah et al. (53), but we do not know if that is a result of better intrinsic mixing with a flow-through system or can be explained by other methodologic or patient differences. Stephen et al. (58) compared intermittent with recirculated peritoneal dialysis in human subjects, and the clearance results were inconsistent. There was one clear example of streaming produced by poor catheter placement, and the average flow rates were not the same in the two methods.

Possible support for an improved PA comes from a study in 50- to 55-lb dogs (57). Catheters were placed in each lower abdominal quadrant, and dialysate was recirculated through an adsorbent cartridge at flow rates from 66 to 250 mL/minute. Clearances of urea and creatinine approximately doubled over this interval. Our analysis of their data suggests that the increase is more than could be accounted for by the additional dialysate alone, so that there may have been an increase in the underlying PA resulting from the larger recirculating flow, but a rigorous analysis is not possible.

Reciprocating systems have a certain appeal because of their simplicity and easy applicability to the clinical setting. In the rat, studies were conducted comparing 25-mL exchanges of dialysate with a 25-mL intraperitoneal volume and rapid 5-mL exchanges superimposed to produce the same average flow rate (60). The reciprocating technique increased urea clearance by 29% and inulin clearance by 38% after 60 minutes, with a further increase in inulin clearance to 100% above the baseline after 120 minutes. The reason for this further increase is not clear, and the investigators did not attempt to reproduce the baseline values to determine if there had been a change in the peritoneal transport characteristics. These changes in clearance should be compared with the potential increase of a factor of 3 or 4 in functional area discussed above.

We note that an abstract (61) reported some data on the effect of simply having patients roll side to side six times immediately following dialysate inflow. There was a small increase in the dialysate-to-plasma concentration ratio at 4 hours for urea, a small but not statistically significant increase in this ratio for creatinine, and a significant decrease in the mean coefficient of variation for both solutes. This may result from better mixing with residual volume from the previous exchange so that the relevance to peritoneal drug administration is unclear.

In general, definitive studies have not been conducted on the potential functional peritoneal surface area of human subjects. Moreover, adequate investigations have not been performed on clinically applicable methods to increase exposure of the serosal surface and attached tumor nodules. Such investigations should receive a very high priority because the likelihood exists that much of the residual tumor burden is untreated or undertreated by conventional procedures. While an increased PA would result in a decreased regional advantage based on peritoneal and plasma concentrations, this should be a reasonable trade-off for improved regional tumor exposure.

**References**


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Notes

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