Role of the Liver in Small-Solute Transport During Peritoneal Dialysis

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ABSTRACT

Peritoneal dialysis (PD) is dependent on the transport of water and solutes from the blood capillaries within the tissues that surround the peritoneal cavity. Because of their large blood supply and surface area, the viscera have been considered the most important tissues for PD transport. In animals, however, removal of the gastrointestinal tract decreases PD small-solute mass transfer by only 10 to 27% (9,10).

To investigate the theoretical basis for these observations, a distributed model of peritoneal transport was extended to take into account the transport characteristics of four tissue groups that surround the cavity: the liver, the hollow viscera, the abdominal wall, and the diaphragm. The mass transfer-area coefficient (MTAC) of sucrose for each tissue was calculated from the following:

\[ \text{MTAC} = \frac{1}{D(p_a)} \left( \frac{A}{V} \right) \]

where \(D\) is the effective solute interstitial diffusivity, \(p_a\) is the solute transcapillary permeability-area per unit tissue volume, and \(A\) is the apparent peritoneal surface area of the tissue. Our results for the adult human predict that the MTAC for the liver is comparable to that of all of the other viscera and makes up 43% of the total MTAC for the peritoneal cavity. The predicted MTAC is 4 cm\(^3\)/min (plasma) or 6 cm\(^3\)/min (blood), in good agreement with published values.

It is concluded that the liver is responsible for a major portion of the small-solute MTAC. This also explains the earlier observations in eviscerated animals whose PD transport was likely preserved by intact livers.

Key Words: Peritoneum, capillary transport, mass transfer, mathematical model

Despite a large number of theoretical articles on the subject of small-solute transfer during peritoneal dialysis, all of the published conceptual models portray the peritoneal transport system as a single tissue with one set of characteristic transport parameters. Simple membrane models (1-5) use a single mass transfer-area coefficient (MTAC) to characterize the entire "peritoneal membrane." More complex physiologic models, which calculate diffusion, convection, and transcapillary transport within the tissue space surrounding the peritoneal cavity (6-8), have also failed to account for the variability of the microcirculation in the different peritoneal tissues and have used a single set of parameters to describe these processes. Recent experimental studies (9-11) have demonstrated only small decreases in the MTAC of small solutes after the removal of the hollow viscera, which compose more than half of the available transport surface area (12). These indicate that the peritoneal transport system may be more correctly treated as a collection of different surfaces in its transport function.

We have examined the theoretical mass transfer characteristics of specific peritoneal tissues. We use our previously published "distributed model" (6,7), which simulates solute transport from blood contained within capillaries that are uniformly distributed in each tissue space surrounding the peritoneal cavity. The peritoneal tissue space is divided into four tissue groups, and parameters that characterize each of these tissue groups are estimated from the literature. These parameters are used to calculate the equivalent MTAC for each tissue group. Our analysis shows that the liver, which possesses only 13% of the peritoneal area, may account for nearly half of the small-solute transfer.
METHODS

Model Concept

Our analysis is restricted to the diffusive transport of water-soluble small solutes (molecular weight <5,000 d) across blood capillary endothelia and through the interstitium that separates the blood capillaries from the peritoneal cavity. The body is shown as a single compartment in Figure 1. The volume of the body compartment equals the volume of distribution of the solute in the total body excluding the tissues surrounding the peritoneal cavity. Solute concentration in the body compartment is assumed to equal the mixed venous concentration (Cv). Blood flows from the body compartment through each peritoneal compartment with the rate Q. Lymph flow from each organ system is assumed to be a negligible component of the small-solute transport.

The peritoneal tissues have been grouped into four major compartments. The separation of parietal tissue into two compartments, the diaphragm and the abdominal wall, permits the evaluation of the effect of the removal of either surface on the transport process, as has been done by Rubin et al. (10). Both of these tissues are assumed to have microcirculatory transport characteristics similar to those of skeletal muscle. The liver is separated from the other visceral tissues because of the unique architecture of its microcirculation, i.e., the high permeability of the hepatic sinusoids and the relatively high density of the exchange vessels within the organ. The "hollow viscera" include the stomach and the small and large intestines. These have been found to have similar small-solute concentration profiles (13) and are therefore lumped together in a single tissue compartment.

Each of these compartments receives blood originating in the body compartment; the liver is also perfused by the portal circulation. The blood flows through capillary exchange vessels distributed throughout the tissue and returns to the body compartment. Solute diffuse from each tissue compartment to the peritoneal cavity with a solute mass transfer rate of R. The peritoneal cavity concentration (Cp) is assumed to be uniform. The cavity does not exchange with the body compartment but only with the tissue compartments.

Model Implementation

In order to evaluate the role of specific tissue groups in the diffusive blood-to-peritoneal cavity transport, we define the rate equation of mass transfer, R, for each tissue compartment. The dialysis of small molecules into the peritoneal cavity can be viewed as a process of diffusion from the blood in the exchange capillaries (Figure 2) into the surrounding tissue interstitium and from there into the peritoneal cavity. It is assumed that the blood flow to the peritoneal tissues provides solute to the exchange capillaries at
a rate faster than the ability of the solute to diffuse out of the vessels (14). The transport is therefore limited only by diffusion. For a uniformly distributed capillary network, it is easily shown that the rate of transfer into the cavity from a specific tissue "I" may be calculated from the following equation (6):

\[
R_i = \sqrt{D_e(p_a)A_i(C_B - C_P)} \quad \text{Equation 1}
\]

where \(R_i\) is the transport rate of the solute from the blood to the peritoneal cavity (in micrograms per minute), \(D_e\) is the effective diffusivity of the solute in the tissue (in square centimeters per minute), \(p_a\) is the permeability of the blood capillaries in the tissue (in centimeters per minute), \(A_i\) is the superficial surface area per unit tissue volume (in square centimeters per cubic centimeter), \(C\) is the free solute concentration (in micrograms per cubic centimeter), and the subscripts B and P refer to blood and peritoneal fluid, respectively. The effective diffusivity is equal to the diffusivity in the tissue interstitial space \(D_e\) multiplied by the tissue fractional interstitial space \(\theta_i\) that is available to the solute.

A number of observations may be made about Equation 1. First, the effective diffusivity, capillary permeability, and capillary surface area enter as their square root so that doubling of the capillary permeability, for example, would be expected to be associated with only a 41% increase in mass transfer \(2^{1/2} = 1.41\). Second, the net transport rate is proportional to the superficial area of the tissue. Third, the rate of transport is proportional to the difference in the free concentration of solute between the peritoneal fluid and blood.

Equation 1 serves as the basis for the definition of an equivalent mass transfer coefficient, \(MTC_i\), of the tissue. If there were a thin membrane separating the peritoneal fluid from the blood, the rate of transport would be given by:

\[
R_i = MTC_iA_i(C_B - C_P) \quad \text{Equation 2}
\]

A comparison of Equations 1 and 2 shows that the equivalent mass transfer coefficient can be calculated from:

\[
MTC_i = \sqrt{D_e(p_a)} \quad \text{Equation 3}
\]

Either Equation 1 or 2 can be used to calculate the rate of transfer of a solute from the blood into the peritoneal cavity because they are exactly equivalent. The spatially distributed view of the tissue (Equation 1) provides some insight into the underlying transport mechanisms. It also serves as a natural link to the very large body of literature on capillary physiology and provides a natural framework to incorporate this into descriptions and predictions of peritoneal transport rates.

Equations similar to Equations 1 and 2 can be written for as many types of peritoneal tissue as desirable. Because uptake rates into the various tissue types are parallel processes, they may be summed to provide:

\[
R = [(MTC_LA_L) + (MTC_VA_V) + (MTC_AA_A)]
+ [(MTC_DA_D)](C_B - C_P) \quad \text{Equation 4}
\]

with the subscripts defined in Figure 1.

Equation 4 is usually given simply as:

\[
R = MTAC(C_B - C_P) \quad \text{Equation 5}
\]

where\(MTAC\) is the mass transfer-area coefficient that incorporates all absorbing structures in contact with peritoneal fluid. The \(MTAC\) is a single parameter defined as the sum of the individual tissues \((MTC_i \times A_i)\), as indicated by a comparison of Equations 4 and 5.

**RESULTS**

In order to calculate the rates \(R_i\) of the solutes shown in Figure 1, transport parameters such as the mass transfer-area coefficient \((MTCA_i)\) for each solute and each organ system must be determined. We have estimated values for \(MTCA_i\) in Table 1 for sucrose (molecular weight, 342 d), which should transport from the blood to the peritoneal cavity at a rate between that of creatinine (molecular weight, 118 Volume 5 • Number 1 • 1994

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**TABLE 1. Adult human parameters for sucrose*\)**

<table>
<thead>
<tr>
<th>Tissue</th>
<th>(a_i)</th>
<th>(p_a)</th>
<th>(D_e)</th>
<th>(\theta_i)</th>
<th>(MTC_i)</th>
<th>(A_i)</th>
<th>MTCA</th>
<th>Fraction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(cm²/cm³)</td>
<td>(cm/min \times 10⁴)</td>
<td>(cm²/min \times 10⁴)</td>
<td></td>
<td>(cm²/min \times 10⁴)</td>
<td>(cm²)</td>
<td>(cm³/cm² min)</td>
<td>(%)</td>
</tr>
<tr>
<td>Liver</td>
<td>250</td>
<td>238</td>
<td>3.3</td>
<td>0.14</td>
<td>16.6</td>
<td>1056</td>
<td>1.75</td>
<td>43</td>
</tr>
<tr>
<td>Hollow Viscera</td>
<td>70</td>
<td>24.7</td>
<td>3.3</td>
<td>0.21</td>
<td>3.5</td>
<td>5432</td>
<td>1.90</td>
<td>47</td>
</tr>
<tr>
<td>Abdominal Wall</td>
<td>70</td>
<td>24.7</td>
<td>3.3</td>
<td>0.12</td>
<td>2.6</td>
<td>880</td>
<td>0.23</td>
<td>6</td>
</tr>
<tr>
<td>Diaphragm</td>
<td>70</td>
<td>24.7</td>
<td>3.3</td>
<td>0.12</td>
<td>2.6</td>
<td>632</td>
<td>0.16</td>
<td>4</td>
</tr>
<tr>
<td>Overall MTAC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4.04</td>
<td></td>
</tr>
</tbody>
</table>

* Abbreviations: \(a_i\), capillary surface density; \(p_a\), capillary permeability; \(D_e\), effective interstitial diffusivity; \(\theta_i\), fraction of the tissue available to solute; \(MTC_i\), mass transfer coefficient; \(A_i\), measured peritoneal surface area; \(MTAC\), mass transfer-area coefficient for entire peritoneum.
The values for $A$ are taken from Rubin et al. (12). The areas have been scaled to a 70-kg body wt by the factor $(\text{body weight})^{0.7}$ (15). MTAC can be estimated from Equation 3, the expression for a diffusion-limited solute transporting in a distributed system.

Values for $p$ and $a$, for the liver in Table 1 have been taken from Crone (16), with the $p$ values recalculated to a plasma concentration basis to account for the extracellular distribution of sucrose and a hematocrit of 0.4. Because the “hollow viscera” are chiefly the stomach and intestines and because the serosal side of these viscera is made up of circular layers of muscle, their capillary transport characteristics are assumed to be equal to those of the hind limb muscle (16). These same values are used for the diaphragm and abdominal wall. Values for $D_\omega$, the diffusivity in the interstitial space, are estimated from Schultz and Armstrong (17) and Flessner et al. (18).

The interstitial fractions ($\theta$) for sucrose have been obtained from values for EDTA, which has a molecular size equivalent to that of sucrose (19). Values for the liver and viscera were taken directly from the article. Values for the abdominal wall and diaphragm have been equated to those for skeletal muscle.

Table 1 reveals the important of the specific tissue groups to peritoneal transport. The calculated values of MTAC demonstrate that the MTAC of the liver is approximately five times that of the hollow viscera and seven times that of the parietal tissues. After each MTAC is multiplied by the apparent area for that tissue group ($A_i$), the liver makes up an estimated 43% of the total MTAC (traditional mass-transfer area coefficient = 4.04 cm$^3$/min). Because of its large surface area, the “hollow viscera” group contributes an estimated 47% of the total MTAC. The abdominal wall and diaphragm make up 6 and 4% of the MTAC, respectively.

DISCUSSION

All existing conceptual and mathematical models of transport during peritoneal dialysis have simplified a complex system of tissues by assuming that it can be equated to a single tissue system with a single set of transport parameters. We have challenged that view by using our “distributed model” and existing physiologic data to calculate parameters that characterize the mass transfer of individual peritoneal tissues. We have found that the liver and hollow viscera are each responsible for nearly one-half of the mass transfer of small solute, with the parietal tissues playing a minor role. The calculated MTAC for sucrose was 4.0 mL/min (6.0 mL/min on the basis of blood concentration), which may be compared with the measured value of 6.0 mL/min (20) and which lies between the measured MTAC for glucose of 13 mL/min (3) and the value for inulin of 2.7 mL/min (3).

Our analysis is based on the assumption that blood flow is not a limiting factor in transport. Alternative sources of data (21) indicate that liver capillaries may have much higher permeabilities to small solutes than those found by Crone (16). The rates of mass transfer across hepatic sinusoids may become so rapid that the transfer of small solutes is limited by blood flow. As outlined in our previous work (6), in order to estimate the mass transfer coefficient for the case of blood flow limitation, the local blood flow per unit volume of tissue ($q$) may be substituted for “$pa$” in Equation 3. Using Crone’s value for liver perfusion, recalculated to plasma flow ($q = 0.47$ mL/min per cubic centimeter), the MTAC_{L} is calculated to be $15 \times 10^{-4}$ cm/min, which is close to the MTAC_{L} value given in Table 1. The proximity of the two values for MTAC_{L} indicates the possibility of blood flow limitations in the transhepatic transfer of small solutes during dialysis. This finding also means that the liver plays a major role in peritoneal dialysis, no matter which limiting assumption is made concerning the transport.

The fact that the liver has a major role in peritoneal solute transfer helps to explain the experimental observations of solute clearance from the peritoneal cavity of animals after the removal of the hollow viscera. Rubin and colleagues carried out studies in rats (9) and in dogs (10) in which they measured solute clearance rates from the peritoneal cavity during dialysis and then repeated the measurements after the entire gastrointestinal tract was removed. They found that evisceration reduced the clearances or the MTAC for urea, glucose, or inulin by 10 to 27%, despite the removal of approximately 60% of the total peritoneal surface area. After covering the abdominal wall with plastic in order to prevent contact with the dialysate, they found no observable changes in the MTAC of either intact or eviscerated rats (9). Fox et al. (11) observed significant decreases in the transport of creatinine in rabbits after evisceration; when the eviscerated animals were subjected to abdominal compression, the MTAC returned to control values. This suggested that the compression of the abdomen restored contact between the dialysate and the source of solute. The well-perfused organ common to these evisceration experiments in all three species was the liver.

Although our model does not attempt to account for the altered physiology of eviscerated animals, it does help to explain the puzzling results. As shown in Table 1, the removal of the abdominal wall surface reduces the total MTAC by approximately 6%, which is likely undetectable in dialysis experiments in rats (9). The removal of the hollow viscera would reduce
the MTAC, but in a much smaller proportion than their share of the total surface. If there were no physiologic changes after evisceration, we would anticipate a decrease in the MTAC of 47%. However, Rubin et al. (22) showed that blood perfusion in the liver of rats increased more than fourfold above control values after evisceration, whereas there were no significant changes in perfusion in the diaphragm and abdominal wall. Pietrzak et al. (23) have raised the possibility that the large increase in hepatic blood flow may offer an explanation of Rubin’s transport data. Our theoretical evaluation has demonstrated the possibility of a blood flow limitation in the transhepatic transfer of small solutes. The increased hepatic perfusion may have increased the liver MTC to compensate for the loss of the hollow viscera from the transport process. A second explanation for the apparent compensatory rise in the MTC x A values of the remaining surfaces might come from the findings of Fox et al. (11), who suggested the importance of fluid contact with the peritoneal surface. The redistribution of fluid to areas not accessible before evisceration may have provided a compensatory increase in the transport area and in the overall MTAC.

The thesis that the liver is a major source of small-solute peritoneal transport presents some interesting clinical possibilities. If transhepatic transport is limited by blood flow, variations in the MTC, and in the overall MTAC might occur during periods of altered portal flow such as fasting or feeding. A small dwell volume or a standing position may decrease the total area of liver in contact with dialysate; this would result in a decrease in liver MTC, A, and the overall MTAC, as suggested by the study of Fox et al. (11). The pharmacokinetics of the ip administration of drugs such as insulin or antibiotics are very dependent on their route of absorption from the cavity; direct absorption into the liver may significantly alter their metabolism. The scientific and clinical implications of the role of the liver in peritoneal dialysis demand confirmatory experimental research.

REFERENCES