USE OF THE DECONVOLUTION PRINCIPLE IN THE ESTIMATION OF ABSORPTION AND
PRE-SYSTEMIC INTESTINAL ELIMINATION OF DRUGS

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ABSTRACT:
The deconvolution principle was used to evaluate the extent of absorption and first-pass elimination of selected drugs. In the first example, deconvolution of the portal blood profiles of etretinate (ET, a synthetic retinoid) indicated that there was significant gut-wall conversion of ET to acitretin (ETA, the primary metabolite of ET) during a 60-min intestinal perfusion of ET. In the second example, deconvolution was used to confirm that the extent of carbovir disappearing from the gastrointestinal lumen was matched by the extent of carbovir appearance in the portal blood. Thus, deconvolution has several important applications in the study of absorption and intestinal first-pass metabolism.

One approach to the determination of extraction by an eliminating organ entails an area under the blood concentration-time curve (AUC) analysis. This may be achieved by administration of drug by multiple routes followed by sampling at a single site (the “multiple site input” approach). Alternatively, administration of the drug at a single site followed by sampling from multiple sites (the “multiple site sampling” approach) (1) may be used. The extraction efficiency for the eliminating organ is then estimated by the ratio of the appropriate AUCs (1).

An accurate determination of AUC necessitates the collection of samples until the concentration-time profile is well within the terminal elimination phase. This in turn requires extended blood sampling times for drugs with long elimination half-lives. In smaller animals such as rats, frequent sampling from multiple sites over a long period of time is impractical. The use of other techniques such as the Wagner-Nelson and the Loo-Riegelman analyses requires specific compartmental restrictions to be placed on the disposition of the drug (2).

The use of deconvolution theory to delineate the absorption and gut-wall metabolism of drugs is presented here. This method of analysis provides an advantage for those drugs for which multiple sites of measurement are restrictive and for experimental protocols that do not allow for extended blood sampling. In addition, no compartmental model specification is required. Two examples are presented.

In the first example, deconvolution theory was used to generate an estimate of the fraction of orally absorbed etretinate (ET) escaping gut-wall metabolism ($f_g$). ET, a synthetic analog of the fat-soluble vitamin A, experiences variable absorption from the intestine as well as significant first-pass elimination. Acitretin (ETA) is the primary active metabolite of ET. Both retinoids (fig. 1) are currently on the market for the treatment of psoriasis, and ET has been studied in clinical trials for cancer chemoprevention and chemotherapy (3). The $in situ$ intestinal perfusion of ET in mixed micelles of sodium taurocholate and egg phosphatidylcholine resulted in a steady-state loss of greater than 80% from the lumen (4). Very low levels of ET were observed in the systemic circulation following intestinal perfusions, but ET and high levels of ETA were detected in the portal blood. An estimate of the extent of gut-wall metabolism of ET during its intestinal absorption from mixed micelles was desired. However, because of the large volume of distribution and long terminal half-life for ET, blood sampling for long periods post-perfusion were required for an AUC approach. Deconvolution of portal blood concentrations was explored to determine the extent of gut-wall metabolism of ET.

The second example involved carbovir [(-) -carbocyclic 2',3',3'-dideoxy-2',3'-didehydroguanosine, CBV, fig. 1] CBV is a carbocyclic nucleoside with demonstrated in vitro activity against the human immunodeficiency virus (5). In rats, the oral bioavailability of CBV is only 20% (6), but CBV does not undergo significant first-pass metabolism in either the liver or intestine (7). This suggested that poor intestinal absorption was responsible for the poor oral availability of CBV in the rat.

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2 Present address: 3M Pharmaceuticals, 3M Center Building 270–3S-05, St. Paul MN 55144-1000.
3 Abbreviations used are: AUC, area under the curve; ET, etretinate; CBV, (--)-carbocyclic 2',3',3'-dideoxy-2',3'-didehydroguanosine; PC, phosphatidylcholine; HPLC, high performance liquid chromatography.

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In the present work, the fraction of intestinally perfused carbovir that appeared in the portal vein during an \textit{in situ} intestinal perfusion was calculated with the use of deconvolution. These estimates were compared with those obtained from the lumenal disappearance of CBV during the intestinal perfusions.

**Theory**

The convolution principle may be expressed as follows:
\[
C(t) = C_{0}(t) * f(t)
\]

(1)

The response function, \(C(t)\), is obtained by the convolution of the unit impulse function, \(C_{0}(t)\), with the input function, \(f(t)\). Mathematical convolution has been functionally expressed here by the asterisk. The applications of this theory are numerous (8–13).

Under conditions of linearity and time invariance, the transport of drug from a site \(i\) to a site \(j\) can be completely expressed by the three functions in eq. 1. \(C_{i}(t)\) refers to the concentration profile obtained when the drug is placed at site \(i\) and the concentration measured at site \(j\). \(C_{j}(t)\) refers to the concentration profile at site \(j\) obtained after the drug is placed directly at site \(j\), and \(f(t)\) represents the transfer function that governs the movement of mass from site \(i\) to \(j\). The knowledge of any two of these three functions allows a determination of the third one.

Deconvolution is the mathematical inverse of convolution. This refers to the situation where a knowledge of \(C_{i}(t)\) and \(C_{j}(t)\) is used to obtain the input function, \(f(t)\).

**Materials and Methods**

\textbf{Eretinate.} ET and ETA were obtained as gifts from Hoffmann-La Roche Inc. (Nutley, NJ). Sodium taurocholylcholine (NaTC) was purchased from Sigma Chemical Co. (St. Louis, MO) and was recrystallized by a modification of the procedure by Pope (14). Egg phosphatidylycholine (PC, lecithin) was purchased from Avanti Polar Lipids (Alabaster, AL). PC was stored at 4°C under nitrogen and protected from light. Retinyl acetate and HEPES (N-[2-hydroxyethyl]piperazine -N’-[2-ethanesulfonic acid]) were obtained from Sigma. All other reagents were reagent grade or better. All procedures were carried out under yellow light to prevent photodegradation of the retinoids.

Mixed micelles containing ET (100 \(\mu g/ml\)) were prepared with 39 mM NaTC and 30 mM egg PC by the simultaneous lyophilization of PC with ET, followed with the addition of NaTC dissolved in buffer. Details for the procedure described previously (4). A 22 G, 1 in., Jelco iv catheter (Criticon Inc., Johnson & Johnson Co., Tampa, FL) was directly inserted into the portal vein. The needle was withdrawn, and once blood was seen emerging from the catheter hub, the catheter was connected to a piece of Intramedic polyethylene (PE-20, Clay Adams, Parsippany, NJ) tubing. This allowed for sampling of portal blood. The PE-20 tubing and the catheter unit were filled with pre-warmed (37°C) heparinized saline (10 units/ml of heparin). The sheath of the catheter was secured to the portal vein wall with two drops of cyanoacrylate adhesive.

The jejunal segment was perfused with the mixed micellar solution of ET (100 \(\mu g/ml\)) at 0.35 ml/min with the aid of a compact infusion pump (Harvard Apparatus, South Natick, MA). Outflow samples were collected at 10-min intervals during the 60-min \textit{in situ} intestinal perfusion. Blood samples of 200 \(\mu l\) were withdrawn from the portal vein at times during the perfusion that were generally at the midpoint of the perfusion collection interval. The withdrawn blood was replaced with 200 \(\mu l\) of heparinized saline. Two hundred microliters of the withdrawn blood were pipetted into Vacutainer glass tubes containing heparin. The tubes were gently vortexed and frozen until the time of analysis. At the end of 60 min, the perfusion was stopped, and the leftover perfusate in the jejunum was flushed with about 10 ml of blank saline. The segment was then flushed with approximately 10 ml of air to clear the segment of all fluids. At the end of the experiment, the jejunal segment was separated from the surrounding vasculature. It was cut open, and mucosal and intestinal cell scrapings were collected with the aid of a glass slide. The scrapings were weighed and frozen until analysis.

\textbf{Unit impulse dosing.} The unit impulse dosing was carried out by giving a bolus dose of ET into the portal vein with subsequent sampling of the same site. Rats (\(N = 2\)) were given an intraperitoneal bolus of 1 mg ET. A separate group of rats (\(N = 3\)) received an intraportal dose of 1 mg ETA. Because of the very poor water solubility of ET (15), the retinoids were each solubilized with 0.714 mg/ml hydroxy-propyl-\(\beta\)-cyclodextran (Pharmaceut, Inc. Alachua, FL). A 1 mg dose was selected to ensure that the blood concentrations of ET and ETA were comparable with those obtained following the intestinal perfusion of ET in mixed micelles. The rats were anesthetized, and a Jelco iv catheter was placed into the portal vein directed toward the liver and secured with two drops of cyanoacrylate adhesive. PE-10 tubing was inserted through the catheter and into the portal vein lumen, and the ET bolus dose was administered through this tubing. At the end of the dosing (1.5 min), the PE 10 tubing was flushed with heparinized saline (10 units/ml heparin). The entire PE-10 tubing was then removed and immediately replaced with PE-20 tubing that could be used later for blood sampling. This ensured that there was no contamination from the bolus dose during blood sampling. The first portal vein blood sample was collected at least 3 min after injection of the bolus to ensure that there was adequate time for the mixing and distribution of the injected dose.

\textbf{Analytical methods.} ET/ETA were extracted from the whole blood samples by modification of a method previously reported (16, 17), with ether replacing acetonitrile/1-butanol as the organic extracting solvent. The recoveries of ET and ETA from rat whole blood were 99% and 91%, respectively. The HPLC assay used for analysis of the samples was reported earlier (4). A sensitivity of 0.005 absorbance unit full scale and a typical injection volume of 45 \(\mu l\) was used on the C18 column. The HPLC assay for the analysis of ET/ETA extracted from whole blood was validated for precision and accuracy (coefficient of variation \(\leq 16\%) at all concentrations) (18).

\textbf{Data analysis.} The fraction of perfused drug that disappeared from the jejunum (\(f_{j}\)) was as follows:
\[
f_{j} = 1 - \frac{X_{\text{out}}}{X_{n}}
\]

(2)

where \(X_{\text{out}}\) is cumulative amount of drug presented to the intestine and \(X_{n}\) is cumulative amount of drug that leaves the intestine unabsorbed.

The fraction of the drug escaping gut-wall metabolism (\(f_{g}\)) was given as follows:
\[
f_{g} = 1 - \frac{X_{p}}{X_{n}}
\]

(3)

where \(X_{p}\) is gut-wall extraction ratio and \(X_{n}\) is cumulative amount of drug appearing in the portal vein.

Based on metabolite concentration in the portal vein, \(f_{g}\) could also be determined by the following method:
\[
f_{g} = \frac{X_{n,m}}{X_{n} - X_{\text{out}}}
\]

(4)

where \(X_{n,m}\) is cumulative amount of metabolite appearing in the portal vein.

To use eq. 4, the following must be assumed: 1) all of the drug that disappears from the gut lumen but does not appear in the portal vein is metabolized and 2) there is no parallel or sequential metabolism occurring in the gut wall.

The extraction ratio calculated according to eq. 3 or 4 is the time-averaged value of the ratio over the period of drug sampling.
The cumulative amount of drug presented to the intestine during the course of the intestinal perfusion \(X_{in}\) is given as follows:

\[
X_{in} = Q \cdot C_{in} \cdot t
\]  

(5)

where \(Q\) (ml/min) refers to the perfusion flow rate, \(C_{in}\) (\(\mu\)g/ml) refers to the total concentration of ET within the mixed micelles, and \(t\) refers to the period of perfusion (60 min for these experiments). The value for \(Q\) was obtained by plotting the volume of perfusate remaining in the syringe as a function of time. The slope of the line of regression for this plot provided the best estimate for the actual perfusion flow rate.

From the analysis of the luminal data, it was possible to determine the total amount of drug that disappeared from the jejunum during each 10-min perfusion interval \((X_{dis})\) as follows:

\[
X_{dis} = X_{out} - X_{in}
\]  

(6)

\(X_{out}\) refers to the amount of ET in the perfusion outflow from the intestine, gravimetrically corrected for water flux during each 10-min interval. \(X_{in}\), the cumulative amount of drug that disappears from the jejunum \((X_{in} - X_{out})\) during the perfusion, can be determined by summing the individual \(X_{dis}\) values over the total perfusion period.

To determine \(X_p\), the portal blood profiles (the impulse response data) of rats receiving an intestinal lumen perfusion of ET were deconvolved with the use of the unit impulse profiles. PCDCON was used for the deconvolution (19). First, the impulse response data were fit with the interpolating spline option (19). The unit impulse data were then fit with a polyexponential function in Kaleidograph (version 3.0). A biexponential fit was found to be adequate. PCDCON directly provided the profile of the cumulative amount of drug metabolite appearing in the portal vein with time, \(X_p\) (or \(X_p,m\)). Eqs. 2–4 were then used to determine the fraction of perfused drug disappearing from the lumen and the fraction of absorbed drug escaping gut-wall metabolism.

**Carbovir.** CBV was obtained as a gift from Glaxo, Inc. (Research Triangle Park, NC). Male Sprague Dawley rats weighing 250–300 g, obtained from Bio-Labs (St. Paul, MN), were used in the intestinal absorption studies.

**Impulse response dosing.** The intestinal perfusion procedure was identical to that described for ET experiments. CBV was perfused \((N = 12)\) through either a jejunal or ileal segment in Krebs-Henseleit buffer at a concentration of 50 \(\mu\)g/ml and a perfusion flow rate of 0.05 ml/min. In contrast to the portal vein sampling for the ET studies, the femoral vein was cannulated with PE-50 tubing to obtain blood samples during the intestinal perfusion experiments (20). Since blood samples were not collected after the perfusion had stopped, an AUC methodology was not used.

**Unit impulse dosing.** The surgical procedure for the unit impulse animals \((N = 3)\) was the same as that for the impulse response dosing experiments except that the intestine was not incised nor was perfusion of the lumen carried out (20). The femoral vein was cannulated for blood sampling. The hepatic portal vein was accessed for CBV dosing by cannulation of the pyloric vein with PE-50 tubing. A bolus dose of 150 \(\mu\)g of CBV in normal saline was administered into the portal vein followed immediately by a 60-min infusion of approximately 13\(\mu\)g/kg/min. The blood samples were extracted by a solid phase extraction procedure and analyzed by HPLC as described elsewhere (21, 22).

**Data analysis.** As in the previous example, PCDCON was used for performing the deconvolution (19). The unit impulse data were fit by a polyexponential function. A biexponential function was previously found to be adequate to describe CBV disposition in rats after an iv dose (20). The concentration time course for a drug administered as an intraportal bolus followed immediately by an intraportal infusion is given by the following equation:

\[
C = \left[\frac{D_c(k_2 - \alpha)}{V_c(\beta - \alpha)}\right] e^{-at} + \left[\frac{D_c(k_2 - \beta)}{V_c(\alpha - \beta)}\right] e^{-bt} + \left[\frac{R_c(k_2 - \alpha)(1 - e^{\alpha t})}{\alpha V_c(\alpha - \beta)}\right] e^{-at} + \left[\frac{R_c(k_2 - \beta)(1 - e^{\beta t})}{\beta V_c(\beta - \alpha)}\right] e^{-bt}
\]  

(7)

where \(D_c\) and \(R_c\) refer to the intraportal bolus and the intraportal infusion rate, respectively, \(V_c\) is the volume in the central compartment, \(\alpha\) and \(\beta\) are rate constants, and \(T\) is the duration of infusion. The unit impulse data were fitted to eq. 7 to retrieve parameter estimates for \(V_c\), \(k_2\), \(\alpha\), and \(\beta\), which were used to calculate corrected values for \(A\) and \(B\) for a 150-\(\mu\)g bolus of CBV (20). The estimates for \(\alpha\), \(\beta\), \(A\), and \(B\) were used as the unit impulse parameters.

The response function was characterized for CBV from the femoral blood profiles obtained during the intestinal perfusion of the drug. The impulse response data were fitted with the interpolating spline option. The impulse function obtained by deconvolution then corresponded to the transport rate for CBV from the intestinal lumen to the portal vein. This rate of transport (estimated by the deconvolution process) was integrated over the time period of the intestinal perfusion to obtain the cumulative amount of CBV that reaches the portal vein, \(X_{p,CBV}\). The \(f_{ac}\) was then calculated for CBV as follows:

\[
f_{ac,CBV} = \frac{X_{p,CBV}}{X_{in,CBV}}
\]  

(8)

where \(X_{in,CBV}\) refers to the cumulative amount of CBV perfused through the intestinal lumen and was calculated with eq. 5 as in the previous example. The estimate of \(f_{ac}\) obtained by using deconvolution was compared with the value obtained by using eq. 2, which requires only luminal data. If there is no first-pass removal of CBV by the intestinal wall, the two estimates of \(f_{ac}\) should be similar.

**Results.** Etretinate. Following the intestinal perfusion of ET from mixed micelles, both ET and ETA were detected in the portal vein. It was possible to obtain estimates for the gut-wall extraction using the portal profile for either ET or ETA. However, if the ETA profile was to be used, then the corresponding unit impulse function needed to be characterized with an intraportal bolus of ETA. It was for this reason that 1 mg of ETA was administered as a bolus in some rats.

Fig. 2A shows the portal vein profile for a 1-mg intraportal bolus dose of ET in a rat. There seemed to be a rapid distribution phase for ET. The unit impulse profiles were fitted by a polyexponential func-
tion, and a biexponential equation was adequate for this purpose. The parameters for the biexponential fit are reported in table 1. The mean terminal half-life for ET in the portal vein was approximately 30 min.

Portal blood profiles from rats that had undergone unit impulse dosing with ETA were also fit to a biexponential function (fig. 2B). These estimated parameters are given in table 2. The mean values of the individually fitted parameter estimates of the unit impulse rats were used for deconvolution of the impulse response profiles.

In the impulse response experiments, blood samples were collected from the portal vein, and these concentration profiles were used for deconvolution. The appearance of ET and ETA in the portal vein during the intestinal perfusion of 100 μg/ml ET is shown in fig. 3. The metabolite levels were much higher than those of the parent. PCD-CON directly generated the time profile for the cumulative amount of drug and metabolite appearing in the portal vein, as shown in fig. 4. The curve was continuously rising, indicating that absorption was occurring throughout the 60-min perfusion. The amount of metabolite that appeared in the portal vein exceeded the amount of the parent, indicating substantial gut-wall metabolism.

The deconvolution of the profile in fig. 4 allowed the determination of $X_p$ and $X_{p,m}$. The values for $X_{p,m}$ were corrected for molecular weight to make the amounts equimolar with respect to the parent (ET). For deconvolution based on the parent (ET) profile, the value for the extraction ratio was found to be $0.65 \pm 0.19$ (mean ± SD; table 3). This indicated that there was loss of 65% of the ET molecules between their uptake from the jejunum and their appearance in the portal vein. The ET and ETA in the mucosal cell scrapings at the end of the ET perfusion studies constituted less than 0.5% of the total perfused ET dose. This indicated that there was no accumulation of ET or its metabolite in the gut tissue during the infusion.

When deconvolution was performed based on the metabolite profile in the portal vein, a mean value of $0.51 \pm 0.275$ was obtained for $E_g$ (table 3). There was significant inter-animal variability associated with this value. There was no statistical difference in the value of $E_g$ calculated using the parent or the metabolite profiles ($t$ test, $p$ value < 0.05).

**Carbovir.** Data from the in situ vascularly perfused rat intestine suggested that CBV was not metabolized in the intestinal wall (7). The fraction of the CBV dose that appeared in the hepatic portal vein was determined with the use of deconvolution. This value was compared with the estimate of $f_g$ obtained from analysis of the lumenal disappearance of CBV (eq. 2). A good correlation between the two estimates would confirm that there was indeed no gut-wall metabolism of CBV. In one of the rats in which the ileum was perfused, several lumenal samples were lost, and eq. 2 could not be used. This rat was excluded from further analysis.

Fig. 5 shows the femoral profile for the intraportal dosing (150 μg of bolus followed immediately by a 13 μg/kg-min infusion) of CBV in a representative rat. These profiles were fit to a biexponential disposition function (eq. 7) to retrieve the estimates of $A$, $B$, $a$, and $b$ (table 4). These estimates were then used as the unit impulse parameters.

The CBV concentration in the femoral vein following jejunal perfusion was used as the impulse response function. Lumenal data from these CBV intestinal perfusions have been reported elsewhere (23). PCD-CON was employed to deconvolve the impulse response function with the unit impulse parameters from table 4. This provided the profile of the cumulative amount of CBV appearing in the portal vein during the jejunal perfusion (fig. 6), which was used to determine $X_{e,CBV}$. The estimated values of $f_g$ (using eq. 8) are reported in table 5. Table 5 also provides the estimates of $f_g$ obtained with the use of lumenal data (eq. 2) alone. There was no statistical difference between the $f_g$ values obtained from the two methods. However, there was a difference in the fraction of CBV absorbed as a function of intestinal site (two-way analysis of variance, $p < 0.05$).

**Discussion**

Deconvolution has been used for evaluating the transit of drugs over most biologic barriers. Most studies have concentrated on study-
The deconvolution of CBV profiles from intestinal perfusions provided an estimate of intestinal extraction ratio. However, the high interanimal variability observed with the use of the metabolite profile is a concern and may be due to violation of one of the assumptions for the use of eq. 4. The assumption is that there is no parallel or sequential metabolism occurring in the gut wall. If the parent molecule is not exclusively converted to the measured metabolite or if the measured metabolite is sequentially converted to another chemical species, then the use of the metabolite profile will underestimate the gut-wall extraction of the drug. Although the metabolic profile for ET metabolism in the gut wall has not been studied, the possibility of the sequential metabolism of ETA cannot be eliminated. The glucuronidation of ETA has been reported to occur in the liver (16).

The conversion of ET to ETA is probably mediated by retinyl esterases present in the intestinal brush border. The activity of one of the major classes of intestinal retinyl esterases is bile salt dependent (24). In studies carried out with rat brush border membrane vesicles, the rate of hydrolysis of shorter-chained retinyl esters was particularly accentuated in the presence of the trihydroxy bile salt, NaTC (24). ET is a short-chain retinoid ester, and the NaTC used for the micellar preparation may be stimulating the metabolism of the compound. This accentuation in the presence of short-chained retinyl esters may explain the high level of gut-wall metabolism for ET that was observed during its jejunal uptake from mixed micelles. Although the gut-wall metabolism of ET is significant, it may not have serious pharmacological implications since ETA is the active metabolite of ET.

Deconvolution can also be an advantage for situations where computation of AUCs over long periods of time is impractical, such as for drugs with long half-lives. On the other hand, use of the data from time 0 to t gives information about the drug transit only during that specific interval of time. For example, in the studies reported here, the value of the extraction ratio is a time-averaged value over the period of sampling only. There may be a danger in extending interpretation of the value over longer periods of time or in situations where the disposition of the drug may change, e.g. in case of enterohepatic recirculation at late times after an oral dose.

The present work has extended the use of deconvolution to the evaluation of the intestinal first-pass effect. Deconvolution of portal or metabolite profiles during lumenal dosing of the drug allows an estimate of intestinal extraction ratio. However, the high interanimal variability observed with the use of the metabolite profile is a concern and may be due to violation of one of the assumptions for the use of eq. 4. The assumption is that there is no parallel or sequential metabolism occurring in the gut wall. If the parent molecule is not exclusively converted to the measured metabolite or if the measured metabolite is sequentially converted to another chemical species, then the use of the metabolite profile will underestimate the gut-wall extraction of the drug. Although the metabolic profile for ET metabolism in the gut wall has not been studied, the possibility of the sequential metabolism of ETA cannot be eliminated. The glucuronidation of ETA has been reported to occur in the liver (16).

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The deconvolution of CBV profiles from intestinal perfusions pro-

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**TABLE 3**

<table>
<thead>
<tr>
<th>Deconvolution Based on:</th>
<th>ET (Parent)</th>
<th>ETA (Metabolite)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Profile</td>
<td>Profile</td>
</tr>
<tr>
<td>( f_a )</td>
<td>0.273 ± 0.057</td>
<td>0.273 ± 0.057</td>
</tr>
<tr>
<td>( f_b )</td>
<td>0.354 ± 0.019</td>
<td>0.486 ± 0.275</td>
</tr>
<tr>
<td>( E_t )</td>
<td>0.646 ± 0.191</td>
<td>0.514 ± 0.275</td>
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</table>

Mean ± SD (N = 4).

**TABLE 5**

<table>
<thead>
<tr>
<th>Rat #</th>
<th>Perfusion Site</th>
<th>( f_a ) (Based on Lumenal Data)</th>
<th>( f_a ) (Based on Deconvolution)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBV 43</td>
<td>Jejunum</td>
<td>0.181</td>
<td>0.123</td>
</tr>
<tr>
<td>CBV 44</td>
<td>Jejunum</td>
<td>0.215</td>
<td>0.164</td>
</tr>
<tr>
<td>CBV 45</td>
<td>Jejunum</td>
<td>0.131</td>
<td>0.166</td>
</tr>
<tr>
<td>CBV 46</td>
<td>Jejunum</td>
<td>0.137</td>
<td>0.141</td>
</tr>
<tr>
<td>CBV 47</td>
<td>Jejunum</td>
<td>0.309</td>
<td>0.243</td>
</tr>
<tr>
<td>CBV 48</td>
<td>Jejunum</td>
<td>0.149</td>
<td>0.170</td>
</tr>
</tbody>
</table>

Mean ± SD 0.187 ± 0.062 0.168 ± 0.037

CBV 51 Ileum 0.124 0.225
CBV 52 Ileum 0.339 0.178
CBV 53 Ileum 0.349 0.468
CBV 54 Ileum 0.350 0.470
CBV 56 Ileum 0.297 0.344

Mean ± SD 0.292 ± 0.086 0.337 ± 0.121

There was no significant difference in fa values determined by either method (two-way analysis of variance, significance level set at 0.05).

\( a f_a \) value calculated using eq. 2.

\( b f_a \) value calculated using eq. 8.
vides another application for the technique. When carrying out intestinal perfusion studies and sampling perfusate alone, the question arises as to whether luminal loss of drug correlates with entry into the portal or systemic circulation. In the present study, the unit impulse dose was placed into the portal vein, with sampling in the systemic circulation. The impulse response function was also measured in the systemic circulation. The input function indicated the input into the portal circulation from a luminal dose. Comparison of the drug disappearance from the lumen and its appearance in the systemic circulation indicated that the intestinal wall did not participate in the metabolism of absorbed drug. In the absence of gut-wall metabolism as is the case with CBV, deconvolution provided another check on the extent of absorption of drug from the lumen.

**Conclusions**

The technique of deconvolution has been successfully applied to the determination of intestinal first-pass extraction. In addition, the technique can be used to verify the estimates of the extent of absorption obtained from the luminal disappearance of the drug.

**Acknowledgments.** The authors thank Hoffmann-La Roche and Glaxo Wellcome for the gifts of the retinoids and carbovir, respectively. The authors also acknowledge the technical assistance of Enas Soud and Shaomei Han.

**References**


