Optimizing the Erythromycin Breath Test for Use in Cancer Patients

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ABSTRACT

The erythromycin breath test (EBT) is a putative in vivo probe for drug metabolism by cytochrome P450 3A4 (CYP3A4). Because many anticancer drugs are metabolized by this system, we sought to further develop the EBT as a tool for predicting the clearance, in cancer patients, of drugs metabolized by CYP3A4.

Sixteen adult patients with incurable cancer were studied. The EBT was performed on day 1 and breath sampled after the i.v. injection of 4 μCi of 14C-erythromycin. The breath 14CO2 flux (CER) was estimated at 11 time points over 2 h. On day 2, the EBT was repeated midway through a 10-min infusion of 100 mg of erythromycin lactobionate, and the plasma pharmacokinetics of erythromycin were determined.

The infusion of 100 mg of erythromycin did not modify the EBT results significantly. The values of the conventional EBT parameter CER20min, obtained on day 1 were comparable for most subjects (0.03–0.06% dose/min), with the exception of an individual receiving the known CYP3A4 inducers dexamethasone and phenytoin who returned a value of 0.14% dose/min. There was no significant correlation between any of the conventional EBT parameters and erythromycin clearance. However, two parameters reflecting early emergence of breath radioactivity (1/TMAX and CER3min/CERMAX) correlated significantly with erythromycin clearance (P = 0.005 and 0.006, respectively).

Novel parameters derived from the EBT are significantly correlated with the clearance of erythromycin even in the presence of confounding factors, such as metastatic liver disease, altered protein binding, and comedication. These parameters may enable dose optimization of cytotoxics metabolized by CYP3A4.

INTRODUCTION

Interridividual differences in pharmacokinetics are significant contributors to the variability of both the antitumor activity and severity of side-effects with cytotoxic drugs (1). For carboplatin, for example, the ability to predict the variable renal clearance of the drug and, consequently, the received area under the curve has enabled rational dose selection in individuals (2), resulting in improvements in both drug safety and tumor response.

The majority of drugs are cleared by hepatic metabolism, particularly by the cytochrome P450 mixed function oxidases. The principal hepatic isoform of these oxidases, CYP3A4, is thought to be a significant contributor to the metabolism of ~60% of all drugs (3). Of particular interest in oncology is the role of CYP3A4 in the metabolism of cytotoxic drugs, such as paclitaxel, docetaxel, vindesine, vincristine, irinotecan, topotecan, ifosfamide, cyclophosphamide, and tamoxifen (4). Therefore, a clinically applicable technique capable of predicting CYP3A4-mediated clearance would prove useful in the rational dose selection of many cytotoxic drugs. Presently, doses are mostly selected according to the patient’s BYSA, although there is little scientific rationale for this practice (5).

Several in vivo probes of CYP3A4 have been proposed and their relative merits discussed (3, 6–12). Arguably, the most widely accepted is the EBT (13). Erythromycin is N-demethylated by CYP3A4, and the cleaved methyl group is released as formaldehyde and, eventually, as CO2. The inclusion of a 14C radiolabel on the N-methyl moieties results in the production of 14CO2, which is then exhaled. After the administration of 3–4 μCi of 14C-erythromycin i.v., the rate of release of 14CO2 in expired breath is thought to reflect hepatic CYP3A4 activity (13). Significant correlations have been observed between the 14CO2 flux at a particular time, or its time-integral, with the clearance of drugs with significant CYP3A4 metabolism, such as cyclosporine (14–16), midazolam (8), and others (3). Also, Baker et al. (17) established a correlation between the EBT and docetaxel clearance normalized for BYSA. However, other studies attempting to correlate drug clearance with the EBT have provided negative findings (9, 10, 12), and erythromycin itself has, surprisingly, not been studied. Therefore, whether the EBT can be used as a reliable predictor of the clearance of drugs metabolized by CYP3A4 requires further clarification (18).

In animal studies, it has been shown that the EBT most accurately reflects the induction of CYP3A4 by dexamethasone when additional, unlabeled, erythromycin is coadministered.

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3 The abbreviations used are: CYP3A4, cytochrome P450 3A4; BYSA, body surface area; EBT, erythromycin breath test; AAG, α1-acid glycoprotein; D1, day 1; D2, day 2; LC, liquid chromatography.
with the $^{14}$C-erythromycin (13). This could occur if CYP3A-
mediated drug metabolism of tracer erythromycin (a tracer dose
of 4 $\mu$Ci equates to 0.05 mg of erythromycin) is not identical to
that observed with pharmacologically relevant doses ($\geq 100$
mg). The addition of unlabeled erythromycin could, therefore,
improve the accuracy of the EBT.

For drugs metabolized principally by the liver and with moder-
ate extraction ratios (such as erythromycin), the total body clear-
ance (CL) is approximated by the product of the fraction unbound
in plasma ($f_{UB}$) and the intrinsic clearance (CL$_{INT}$). The latter
represents the drug metabolism activity of the liver expressed as a
clearance. From the presence of $f_{UB}$ in the product, it is evident that
protein binding could be a major confounder of the relationship
between drug clearance and CYP3A4-mediated intrinsic clearance.
This concern is all of the more relevant given that plasma AAG,
which is the major binding protein for many drugs, including
erythromycin (19), is increased significantly in patients with ad-
vanced malignancies (20, 21). The other possible confounder is the
presence of pathways of elimination, such as renal clearance,
biliary excretion, and non CYP3A4-mediated metabolism (12).
Hence, even if the EBT is a good predictor of CYP3A4 activity, the
above listed factors could nullify its usefulness with regards to
predicting total body clearance of drugs. This may be further
exacerbated by the presence of comorbidity and comedication,
which can affect drug metabolism and the EBT (13).

The objectives of this study were to investigate the relation-
ship between the EBT and erythromycin clearance in cancer
patients, and to determine the effects of erythromycin dose and
protein binding on this relationship.

PATIENTS AND METHODS

Clinical Study Design. Sixteen adult patients with incur-
able cancer were enrolled into the study. Patients were eligible
if they had not received chemotherapy within 6 weeks before the
study and were not on medication that could be adversely
affected by the administration of erythromycin. Patients were
excluded if they had prior adverse reactions to erythromycin.
Written informed consent was obtained from all patients, and
the study was approved by the Ethics Committee of the Royal
Prince Alfred Hospital.

The study was carried out as a two-period nonrandomized
design. On D1, a conventional EBT was performed. Fresh plasma
was collected for the analysis of erythromycin protein binding and
time of day may all affect the endogenous production of CO$_2$;
hence, all EBTs were initiated between 9 and 11 a.m. Also, patients
were seated in a semirecumbent position for at least 15 min before
the injection of tracer erythromycin and throughout the breath
collection period.

EBT. The 4-$\mu$Ci dose of $^{14}$C erythromycin (N-methyl-
$^{14}$C, 55 mCi/mmol; NEN Life Science Products Inc, Boston,
MA) was diluted into 5 ml of dextrose saline and loaded into a
5-ml syringe. A low-volume 0.22-$\mu$m sterile filter (Milllex-GV,
Millipore, Bedford, MA) was attached, and the air was chased
through. After obtaining the total weight of the syringe, the dose
was administered as a bolus through the side port of the infusion
set. Breath collection was carried out by blowing through a straw
into 2 ml of capture solution in glass vials. The capture solution
consisted of benzethonium hydroxide (Sigma Chemical Co,
St. Louis, MO) in 50:50 methanol/ethanol v/v to which a trace
of phenolphthalein was added. A change in color from
pink to clear indicated the capture of 1 mmol CO$_2$. Breath
was collected pre-dose and then at 3, 8, 20, 30, 40, 55, 65, 75, 95,
115, and 145 min after the injection of radiotracer. Vials were
capped and stored on ice until 10 ml of scintillant cocktail
(Ultima Gold, Packard, Sydney, New South Wales, Australia)
could be added. The samples were vortex-mixed and left stand-
ning at room temperature in the dark before liquid scintillation
counting (Tricarb 1500, Packard). The flux of exhaled $^{14}$CO$_2$
at each time point ($CER$), expressed as a percentage of dose/min,
was calculated from:

$$CER = \frac{dpm_{sample}}{dpm_{dose}} \cdot 100 \cdot BYSA \cdot 5 \cdot \frac{\Delta weight}{0.05}$$

in which $dpm_{dose}$ was the reading for a 50-$\mu$l aliquot of the
injected solution (made up in capture solution), and $\Delta weight$
was the mass (g) of solution injected. The product of BYSA:5
allows the normalization of total CO$_2$ output of individuals on
the basis of 5 mmol exhaled/min/m$^2$ in resting individuals (13).

The maximum flux, $CER_{MAX}$, and the time at which it occurred,
$T_{MAX}$, were determined directly from observed values.

The areas under the flux curve for the first hour ($AUCER_{0-1h}$)
and extrapolated to infinity ($AUCER_{t_{\to}\infty}$) were estimated by stand-
ard trapezoidal methods. In the case of $AUCER_{t_{\to}\infty}$, extrapolation
was carried out after identifying the terminal log-linear decrease
in flux ($k_{CER}$).

Because the values of $T_{MAX}$ are limited to actual sampling
times, this causes a lack of continuity in this variable. Therefore,
a model-dependent $T_{MAX}$ value ($T_{MAX(model)}$) was also obtained
by first fitting the breath-flux data to the equation:

$$CER = \frac{A \cdot k_s}{(k_s - k)} (e^{-k} - e^{-k_s})$$

in which $A$ is a constant and $k_s$ and $k$ are arbitrary absorption and
elimination coefficients, respectively. This was carried out using
nonlinear regression (22) with Excel 97 (Microsoft Corp, Red-
mond, WA). $T_{MAX(model)}$ was then obtained from:

$$T_{MAX(model)} = \frac{\ln \left( \frac{k_s}{k} \right)}{k_s - k}$$

Erythromycin Pharmacokinetics. On D2, blood sam-
ple (5 ml) were collected from a contralateral cannula into
heparinized containers before, midway, and at the end of the
erythromycin infusion and then 5, 10, 20, 40, 50, 60, 80, 100,
120, 160, 200, 240, 300, and 360 min after. The samples were
immediately centrifuged at 4°C for 10 min, and plasma was
transferred into polypropylene vials, which were stored at
$-70°C$. 
Samples were analyzed using a Shimadzu QP8000 (LC/ mass spectrometry) Spectrometer (Shimadzu Scientific Instruments, Rydalmere, New South Wales, Australia) connected to a Shimadzu LC system via the electrospray interface. Firstly, samples, standards (0.01, 0.1, 1, 5, and 20 μg/ml) and quality controls (0.02 and 10 μg/ml) were extracted using Nexus solid phase extraction columns (Varian Australasia Pty Ltd., Mulgrave, Victoria, Australia) after spiking with 1 μg of the internal standard, oleandomycin. Samples were loaded onto the unconditioned columns, which were rinsed sequentially with 1 ml of water and 1 ml of 20% aqueous methanol and eluted with 1 ml of methanol into 1.5-ml Eppendorf tubes. The eluant was dried under vacuum in a centrifuge (SpeedVac SC200, Savant Instruments, Sydney, New South Wales, Australia) after which it was reconstituted in 100 μl of the LC mobile phase [20 mM ammonium acetate (pH 5.5) mixed 1:1 with acetonitrile, v/v]. The samples were vortex-mixed and centrifuged, and 0.2–10 μl were injected onto the column (Symmetry C-8, 2 × 150 mm, Waters Australasia Pty Ltd., Rydalmere, Australia) using a cooled (15°C) autoinjector. The entire column outflow (0.2 ml/min) was nebulized at 230°C with a N2 flow of 4 liters/min. The probe, curved desolution line, and deflector plate voltages were set at 3.5 keV, −30 V, and 55 V, respectively in positive ion mode. Erythromycin and oleandomycin were monitored as their corresponding [M+H] ions (m/z of 734.7 and 688.6, respectively). Using this method, the mean recoveries of erythromycin and oleandomycin were 64.1 and 81.6%, respectively. Inter- and intraday variability and total accuracy averaged 7.3, 7.7, and 99.0%, respectively, over the range of erythromycin concentrations studied (0.01–20 μg/ml).

The area under the concentration curve (AUC_{0→∞}) and the area under the first moment of the concentration curve (AUMC_{0→∞}) were estimated using the trapezoidal method and extrapolated to infinity. Standard pharmacokinetic parameters, such as total body clearance (CL), volume of distribution at steady-state (Vd_{SS}), and mean residence time (MRT) were calculated from:

\[ CL = \frac{\text{dose}}{AUC_{0→∞}} \]  

\[ MRT = \frac{AUMC_{0→∞}}{AUC_{0→∞}} - \frac{\tau}{2} \]  

\[ Vd_{SS} = \frac{\text{dose}}{AUC_{0→∞}} \cdot MRT \]  

where \( \tau \) is the duration of infusion.

The terminal elimination half-life (t_{1/2z}) was estimated from the log-linear regression of the last five to six time points of the concentration versus time curve.

**Protein Binding of Erythromycin.** Erythromycin binding was investigated in freshly collected plasma at two concentrations, 0.4 and 2.1 μg/ml. Briefly, 9 nCi of ^14^C-erythromycin were added alone or with erythromycin as the free base (ICN Biomedicals Inc., Aurora, OH) to 0.6 ml plasma and incubated at 37°C for 5 min. The incubate was transferred to ultrafiltration devices (10,000 mw cutoff, Centrifree, Amicon Corp., Danvers, MA) and centrifuged in a fixed rotor centrifuge for 7 min. Aliquots (100 μl) of the ultrafiltrate and reservoir were counted by liquid scintillation, and the fraction unbound in plasma (f_{UB}) was calculated as the ratio of the respective dpm counts.

The plasma concentration of AAG was determined using a commercial immunodiffusion kit (NOR Partigen, Dade Behring Inc., Newark, DE).

**Statistics.** The differences in EBT parameters on days 1 and 2 were analyzed by Student’s paired t-tests, except for \( T_{MAX} \) data for which a Wilcoxon Signed Ranks Test was used.
A Student’s paired t test was also used to evaluate the effect of erythromycin concentration on protein binding. Correlations between CL and EBT parameters (CERMAX, CER20, AUCER0-1h, AUCER0-12h, and TMAX) from each day were sought using Pearson’s correlation. The Ps so obtained were corrected for the multiple comparisons using the Dunn-Sidak test. Ps obtained from other correlations were uncorrected except where specified otherwise.

**RESULTS**

Sixteen patients participated in the study. Their characteristics are shown in Table 1. The median age was 57 years, and equal numbers of males and females were recruited. The values of BYSA ranged from 1.48 to 2.40 m². Two female subjects did not complete D2 of the study (lack of successful venous access and personal reasons). Because of a technical difficulty, the exact dose of 14C-erythromycin could not be determined in one and personal reasons). Because of a technical difficulty, the exact dose of 14C-erythromycin could not be determined in one subject on D2. However, the D1 EBT results from these individuals are included in the pertinent analyses.

**EBT.** The values of the EBT parameters measured on the 2 days are shown in Table 2. In general, the values of CERMAX and CER20 were close to their respective medians (±50% of median), with the exception of a subject being treated with both phenytoin and dexamethasone who had the highest values. Statistical analysis did not reveal any significant differences between the 2 days for any of the tabulated parameters. There was a trend toward a reduced TMAX on D2, but this did not reach statistical significance (P = 0.069). Because of the presence of confounding factors (liver disease, comedication, and so forth), the EBT results were not analyzed for gender effects.

**Erythromycin Pharmacokinetics.** The clearance of erythromycin varied ~5-fold between patients and ranged from 10.48 to 47.01 liters/h. The relevant pharmacokinetic parameters are listed in Table 3. There was no significant correlation between clearance and either BYSA or age (P > 0.7). D1 EBT and erythromycin plasma concentration profiles of representative subjects with high and low CL values are shown in Fig. 1.

The fraction unbound of erythromycin ranged from 0.06 to 0.28 and was significantly increased at the higher concentration of erythromycin (P = 0.026). The fUB value for each individual, as used for correlative analyses, was taken as the mean of the two determinations. The fraction unbound was negatively correlated (r² = 0.39; P = 0.017) with plasma AAG (Fig. 2). Erythromycin clearance decreased with increased protein binding, but this was not statistically significant (r² = 0.20; P = 0.11). The volume of distribution at steady-state (Vdss) was strongly correlated with clearance (r² = 0.74; P = 8.7 × 10⁻⁵).

**Correlations of Erythromycin CL and EBT.** There was no significant correlation between any of the conventional breath-test parameters (CER20, CERMAX, AUCER0-1h, AUCER0-12h, and TMAX) on either of the 2 days and the measured erythromycin clearance (r² < 0.22; Dunn-Sidak P > 0.5). Subjects with high clearance values tended to have early emergence of breath radioactivity on D1, and consequently, low TMAX values (e.g., see Fig. 1). This did not apply in the case of the D2 breath-test results, and a possible reason for this is discussed later. CL was negatively and significantly correlated with TMAX (r² = 0.49; Dunn-Sidak P = 0.025). However, the corresponding line of regression indicated that CL would take on negative values for TMAX > 30 min. Because CL is expected to range from 0 to infinity, the correlation between CL and the D1 I/TMAX was investigated and found to be significant also (r² = 0.49; P = 0.005). Using the inverse of the TMAX value estimated from the fitting of the breath-flux data to equations 2 and 3 (TMAX(model)) yielded a stronger correlation (r² = 0.64; P = 0.001). Another indicator of early breath-emergence was CERMAX/CERMAX - which was also significantly correlated with CL (r² = 0.47; P = 0.006).

Plotting the CL data against I/TMAX(model) (Fig. 3) revealed that most were well described by linear regression, with the exception of a single outlier (Studentized Residual = 4.3). Removal of this outlier yielded the linear regression (r² = 0.85; P = 7.5 × 10⁻⁶) described by:

\[
CL = 552 \times \frac{1}{T_{MAX(model)}} - 12.9
\]

in which TMAX(model) is the model-interpolated value of time at which maximal radioactivity flux occurred.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Breath-test parameters on day 1 and day 2 of study</th>
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<tbody>
<tr>
<td>CER20</td>
<td>CERMAX</td>
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<tr>
<td>% dose/min</td>
<td>% dose/min</td>
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<tr>
<td>D1</td>
<td>D2</td>
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<tr>
<td>Minimum</td>
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<tr>
<td>Maximum</td>
<td>0.140</td>
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<tr>
<td>Median</td>
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<table>
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<tr>
<th>Table 3</th>
<th>Pharmacokinetic parameters for erythromycin (100 mg) administered i.v. a</th>
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<tbody>
<tr>
<td>CL (liters/h)</td>
<td>Vdss (liters)</td>
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<tr>
<td>Minimum</td>
<td>10.48</td>
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<tr>
<td>Maximum</td>
<td>47.01</td>
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<tr>
<td>Mean</td>
<td>23.75</td>
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<td>SD</td>
<td>10.57</td>
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a n = 14.
DISCUSSION

With the present study, we aimed to investigate the performance of the EBT as a predictor of CYP3A4-mediated drug clearance in cancer patients. Erythromycin was chosen as the reference drug whose clearance we measured and compared with various parameters derived from the EBT. The effect of performing the EBT during an infusion of 100 mg of erythromycin was also investigated. In this study, the median values of both the EBT and erythromycin CL were comparable with those reported for healthy volunteers (10, 23).

The conventionally derived EBT parameters (CER_{20 min}, CER_{MAX}, AUCER_{0-3 h}, and AUCER_{0-\infty}) were not affected by the presence of additional erythromycin in the D2 EBT and were not predictive of erythromycin clearance (CL) on either day. Instead, we found that indicators of early emergence of breath radioactivity (1/T_{MAX}, CER_{3 min}/CER_{MAX}) from the D1 EBT were significantly correlated. Presumably, early emergence reflects rapid hepatic uptake and metabolism of erythromycin, which are requisite for high total clearance. In other words, the 1/T_{MAX} may reflect early drug distribution and elimination rather than just CYP3A4 metabolism.

Interpolating the breath flux data to yield a model-dependent 1/T_{MAX(model)} value resulted in stronger correlations with CL than with 1/T_{MAX} itself. This is likely to be attributable to the continuity of the latter, whereas T_{MAX} values are limited to actual breath sampling times. Because the peak occurred in all cases before 30 min, a modified EBT using 1/T_{MAX} will remain a practical procedure.

The correlations between both 1/T_{MAX} and 1/T_{MAX(model)} and CL identified one subject as an outlier. It is unclear whether this was a random finding or a particular feature of this subject, who is a frequent user of both alcohol and cannabis. Because the production of carbon dioxide from the oxidation of erythromycin is folate-dependent, a reduction in the folate-dependent intermediate step could potentially explain the apparent delay (i.e., low 1/T_{MAX}) in the EBT test results of the outlier. However, the vitamin B12, serum folate, and erythrocyte folate were all within the normal range for this individual, although the serum homocysteine was slightly elevated (25 μmol/liter; normal range, 7–23 μmol/liter), indicating a mild decrease in functional folate status.
The relationship between \( I/T_{\text{MAX}} \) and \( CL \) was not significant using the D2 EBT results. Indeed, there was a shift in the \( T_{\text{MAX}} \) on D2 that varied from subject to subject. Because the EBT was administered midway through the erythromycin infusion, this is likely to represent a protein-binding disequilibrium phenomenon. In any case, in the absence of any effect of the administration of 100 mg of erythromycin on the EBT, it is possible to use the conventional tracer-only EBT without coadministered erythromycin in future studies.

Although the conventional EBT was not predictive of erythromycin \( CL \), there was some evidence of relationship to CYP3A4 activity. A subject receiving the known inducers phenytoin and dexamethasone had a \( CER_{90\text{min}} \) value some 3.5 times the median. Also, a subject with extensive metastatic involvement of the liver (as reflected by significantly abnormal liver function tests) had one of the lowest \( CER_{90\text{min}} \) values (0.028%/min) and a low erythromycin \( CL \) (10.5 liters/h). However, the “induced” subject had a relatively modest erythromycin \( CL \) (32.5 liters/h), and the subject with the highest \( CL \) value (47.0 liters/h) actually had a low \( CER_{90\text{min}} \) value (0.035%/min). It may be that the EBT does correlate with CYP3A4 activity, but because of protein-binding effects and/or the presence of other pathways of elimination, it does not correlate with drug clearance.

Other results show both the \( f_{13B} \) of erythromycin and the plasma concentrations of AAG to be highly variable between subjects but interrelated. The \( CL \) correlated to its volume of distribution (\( V_d \)), which indicates a strong influence of protein binding on the metabolism and disposition of erythromycin. This is in agreement to studies performed in cirrhotic patients, in whom erythromycin pharmacokinetics are modified partly through the altered protein binding of erythromycin (24). Our results indicate that the conventional parameters of the EBT (based on the \( ^{14} \text{CO}_2 \) flux) are likely to be confounded by protein binding. The variability of which may obscure that due to intersubject differences in the activity of CYP3A4. This may be of relevance to EBT studies in other patient populations.

Many anticancer drugs are metabolized by CYP3A4, but there are no readily available techniques for pharmacologically based dosing of individual patients. In cancer patients, our study shows that the EBT is predictive of the clearance of the prototypic CYP3A4 substrate, erythromycin, when using parameters that reflect the kinetics of breath radioactivity. We now intend to prospectively evaluate equations incorporating \( I/T_{\text{MAX}} \) for the clearance of anticancer drugs.

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